THE ESSENTIAL GUIDE FOR THf CARE OF PATIENTS WITH GASTROENTEKOLCGICAL AND HEPATOIOCICAL DISEASE

OXFORD HANDBOOK OF GASTROENTEROLOGY AND HEPATOLOGY

Stuart Bloom | Gcorgo Webster | Daniel Marks

Thoroughly revised, now with & tfcdicated section On endoscopy. reflecting the many advance? In this key area

Comprehensive A–Z QF conditions alEaws Fast access to focused key Informarkwi about the range of conditions **Thai** may be encountered

Updated to highlight key current patient Issues, intruding communication, palliative care, use of evidence, and parent-ten tred outcomes

THIRD EDITION • THIRD EDITION •

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Oxford Handbook of Gastroenterology and Hepatology

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OXFORD HANDBOOK OF

Gastroenterology and Hepatology

THIRD EDITION

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We learnt a lot from reading other volumes in the Oxford Handbook series with overlapping content (the *Oxford Handbook of Clinical Medicine* and the *Oxford Handbook of Tropical Medicine* in particular). We are grateful to our colleagues at University College London Hospitals and UCL, who kindly reviewed the book, and particular thanks to Daniel Marks, Ailsa Hart, and Raza Malik, who carefully read, edited, and improved the text. Thanks, as ever, also go to our families who remained incredibly supportive throughout, even with the realization that writing a little book never takes a little time!

Finally

So here's the result, and we hope you find this book of practical use, fun, and informative. We would welcome feedback, which can be directed to us via the OUP website www.oup.co.uk/academic/medicine/handbooks/comments

Stuart Bloom and George Webster
University College London Hospitals
2006

Foreword

It is quite remarkable how much information is contained within this handbook, but the authors never forget its primary function—to provide clear and easily available evidence-based facts. It does not dwell on the evidence, always giving priority to clear management advice, but gives the reader the chance to pursue the background further with a few well-selected references.

The authors manage to make it relevant to all doctors confronted by patients with gastrointestinal symptoms. The handbook will instruct the medical student on the approach to the patient, guide the junior doctor on what do in the night, remind the registrars of their MRCP knowledge, and reassure the senior doctor that the principles of good patient care remain the same. It is nonetheless up to date in the latest therapies, which is important in a specialty with its fair share of '-mibs and -mabs'. In an era where there is often too much information available, it is good to have a resource that is tried, tested, up to date, and produced by gastroenterologists who have the respect of their peers.

Sir Ian Gilmore DL
Director, Liverpool Centre for Alcohol Research
Chairman, Alcohol Health Alliance, UK

Preface to the third edition

We were delighted to be approached by OUP to write a third edition of this text, which has given us an opportunity to take stock and reflect on developments in gastroenterology and hepatology over the past 8 years. It is not an overstatement that there have been transformational advances in both specialties: a profusion of new therapies for inflammatory GI diseases, the evolution of chronic viral hepatitides from often lifelong infections to be managed to potentially curable, and major updates across the board in cancer screening and management algorithms.

In this edition, we have comprehensively reviewed and updated the entire text. As part of this process, we have also:

- Written new Approaches on the management of patients with eating disorders, and post-liver transplant patients.
- Revised the Clinical Practice and Diagnostic section to highlight several patient issues that have come to increased prominence in recent years, including elements of communication, palliative care, and use of evidence, including patient-centred outcomes.
- Broken out the section on endoscopy into a dedicated chapter, which reflects the many advances since the previous edition.
- Comprehensively updated the A–Z section and the Drugs chapter, which now incorporates many new therapies as well as refined advice on how to select between options within a therapeutic class.
- Included additional topics in the Emergencies section on abdominal trauma, bowel obstruction, and major haemorrhage.

To achieve such a comprehensive update, we have been very grateful for the help and support of a number of subspecialty contributors. These include Drs Deepak Joshi, Louise China, Mathena Pavan, Bahman Shokouhi, Mark Samaan and David Graham, without whose input this edition would not have been possible. We are also extremely grateful for the advice and critical appraisal from a number of our colleagues including Dr Rami Sweis, Prof Robert Miller, Dr Karishma Sethi, and Dr Fran Bennett.

We hope that this has resulted in a portable text that remains a useful, up-to-date, and readable primer for clinicians of all grades working in Gastroenterology & Hepatology.

Stuart Bloom, George Webster, and Daniel Marks
University College London Hospital
2021

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Preface to the first edition

Why write another textbook?

There are many excellent textbooks of gastroenterology and hepatology, and many calls on our time. Apart from the fact that the commissioning editor, Alison Langton, asked us very nicely and persistently, a few considerations raised us from our naturally indolent state and gave us the energy to contemplate the task:

- The format and portability of the Oxford Handbooks is attractive and the series has not, to date, included a text on gastroenterology and hepatology. Even with white coats out of fashion, the Handbooks are easily transportable in rucksacks or handbags and do not induce herniae on opening.
- Gastroenterology and hepatology involve many organ systems. Most textbooks are organized anatomically (i.e. start at the mouth and move south), which often relates poorly to how patients present to doctors (e.g. the jaundiced patient—due to hepatitis A, gallstones, or pancreatic cancer?). This may lead to both repetition through the text, and a need for large complicated indexes to help search for relevant information.
- It seemed to us that there is a need for up-to-date information on how to approach both clinical scenarios (e.g. abnormal liver tests; lower GI bleeding) and specific conditions in GI and liver practice, both common and uncommon. This information needs to be organized in such a way that it can be easily obtained in the clinic, on the way to a ward to see a patient referred with an exotic or unfamiliar condition, or when telephoned for advice by a colleague—or a patient.

Who is it written for?

- This book is aimed at all those interested in the presentation and management of patients with gastrointestinal and liver disease. This includes some but not all medical students, most junior doctors training in hospital medicine and in general practice, and all those training in gastroenterology/hepatology, one of the most challenging and fast developing of the medical specialties.
- We hope it will also appeal to many senior doctors immersed in busy practice who may find it useful to be reminded of the salient points of commonly (and less commonly) encountered conditions and problems in the field.
- Finally we hope that in the age of multidisciplinary teams the book will be of value to those working in nursing and professions allied to medicine, particularly clinical nurse specialists and nurse consultants and those involved in pharmaceutical practice and dietetics.

How is it different from other textbooks?

We have organized the book into a series of sections. Underlinings represent an entry in the relevant section and will enable hyperlinking in the electronic version of the book (if it's successful).

- ⚠ **Bold for emergencies** ⚠ A section on GI emergencies offering help on acute management based on clinical priorities.
- ▶ Green for approaches to common clinical problems
  A section on the approach to various clinical problems and scenarios encountered in the clinic and on the wards.
- ➲ Black for A to Z of topics
  Most of the book is dedicated to an A to Z of conditions and problems in gastroenterology and hepatology. This is (to our knowledge) a new way of organizing a text on the subject, but we hope it will enable readers in accessing information. Throughout this section, there are text links to other related topics, and to the emergencies and approaches section, highlighted as they are listed here.
- → SMALL CAPITALS FOR PARTICULAR DRUGS
  An index of drugs commonly used in gastroenterology and hepatology. This is not intended to duplicate or replace information in crucial and authoritative texts such as the *British National Formulary*, but rather to give key facts of dosage, methods of administration, and common cautions, side effects, and interactions. Practice points are also included, drawing on our combined experience in the specialty.

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Symbols and abbreviations

❗	caution
▷	clinical practice and diagnostics
▶	see *approaches* section
➔	*see emergencies section*
▲	see *emergencies* section
→	see *drugs* section
↑	raised
↓	lowered
🖱	online reference
💣	controversial topic
∴	therefore
αFP	alpha-fetoprotein
γGT	gamma-glutamyl transpeptidase
5-ASA	5-aminosalicylate
5-FU	fluorouracil
5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine (serotonin)
AAD	antibiotic-associated diarrhoea
Ab	antibody
ACE	angiotensin-converting enzyme *or* antegrade colonic enema
ACTH	adrenocorticotrophic hormone
ADH	antidiuretic hormone
AF	atrial fibrillation
AFB	acid-fast bacillus
AFLP	acute fatty liver of pregnancy
AGA	American Gastroenterology Association
AIDS	acquired immune deficiency syndrome
AIH	autoimmune hepatitis
AIP	acute intermittent porphyria *or* autoimmune pancreatitis
AKI	acute kidney injury
ALA	amino-laevulinic acid *or* amoebic liver abscess
ALF	acute liver failure
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	anti-mitochondrial antibodies
AMP	adenosine monophosphate
ANA	anti-nuclear antibody
ANC	acute necrotic collection
AP	acute pancreatitis
APC	adenomatous polyposis coli (gene) *or* argon plasma coagulation
apo-B	apolipoprotein B
APTT	activated partial thromboplastin time
APUD	amine precursor uptake and decarboxylation (cells)
ARR	absolute risk reduction
ASA	American Society of Anesthesiology
ASD	atrial septal defect
ASM	anti-smooth muscle (antibodies)
AST	aspartate aminotransaminase
ATLS	Advanced Trauma Life Support
AUDIT	Alcohol Use Disorders Identification Test
AV	arteriovenous
AXR	abdominal X-ray
AZA	azathioprine
BAM	bile acid malabsorption
BCG	Bacillus Calmette-Guérin
BCS	Budd–Chiari syndrome
bd	twice a day
BDS	bile duct stones
β-HCG	beta human chorionic gonadotrophin
BMD	bone mineral density
BMI	body mass index
BMR	basal metabolic rate
BMT	bone marrow transplant
Bn	bilirubin
BNF	*British National Formulary*
BP	blood pressure
BSG	British Society of Gastroenterology
Bx	biopsy
cAMP	cyclic adenosine monophosphate
CBD	common bile duct

CDAD	*Clostridioides difficile*-associated diarrhoea
CDAI	Crohn's disease activity index
CDC	Centers for Disease Control (US)
CDEIS	Crohn's disease endoscopic inflammation score
CE	capsule endoscopy
CEA	carcinoembryonic antigen
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CGD	chronic granulomatous disease
CHB	chronic hepatitis B
CKD	chronic kidney disease
CLE	confocal laser endomicroscopy
CLO	*Campylobacter*-like organisms (test for)
CMV	cytomegalovirus
CNS	central nervous system
CO	carbon monoxide *or* cardiac output
COX	cyclo-oxygenase
CREST	calcinosis–Raynaud's–oesophageal dysmotility–sclerodactyly–telangiectasia (syndrome)
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSU	catheter specimen of urine
CT	computed tomography
CTD	connective tissue disease
CVA	cerebrovascular accident
CVP	central venous pressure
CXR	chest X-ray
CYP	cytochrome P450
DAA	directly acting antiviral
DAEC	diffusely adhering *E. coli*
DBD	donors after brain death
DBE	double-balloon enteroscopy
DCC	deleted in colorectal cancer (gene)
DEXA	dual energy X-ray absorptiometry
DF	discriminant function
DIC	disseminated intravascular coagulation
DILI	drug-induced liver injury
DIOS	distal intestinal obstruction syndrome
DOAC	direct oral anticoagulant
DPL	diagnostic peritoneal lavage
DRE	digital rectal examination
DRESS	drug reaction with eosinophilia and systemic symptoms
DS	Down syndrome
dsDNA	double-stranded DNA
DT	delirium tremens
DU	duodenal ulcer
DVT	deep vein thrombosis
EAggEC	entero-aggregatory *E. coli*
EBV	Epstein–Barr virus
ECG	electrocardiogram
EGC	early gastric cancer
EGF	epidermal growth factor
eGFR	estimated glomerular filtration rate
EGG	electrogastrography
EHEC	enterohaemorrhagic *E. coli*
EHL	electrohydraulic lithotripsy
EIA	enzyme immunoassay
EIEC	enteroinvasive *E. coli*
ELISA	enzyme-linked immunosorbent assay
EMR	endoscopic mucosal resection
ENT	ear, nose, and throat
EPEC	enteropathogenic *E. coli*
EPO	erythropoietin
ERCP	endoscopic retrograde cholangiopancreatography
ESR	erythrocyte sedimentation rate
EST	endoscopic sclerotherapy
ESWL	extracorporeal shock wave lithotripsy
ETEC	enterotoxigenic *E. coli*
EUA	examination under anaesthesia
EUS	endoscopic ultrasound
FAP	familial adenomatous polyposis
FAST	Focused Assessment with Sonography for Trauma
FBC	full blood count
FDG	2-fluoro-2-deoxy-D-glucose
FE1	faecal elastase type 1
FFP	fresh frozen plasma
FGP	fundal gastric polyp
FIT	faecal immunochemical test
FMF	familial Mediterranean fever
FNA	fine-needle aspiration
FNAC	fine needle aspiration cytology

FNH	focal nodular hyperplasia
FOBT	faecal occult blood test
FSH	follicle-stimulating hormone
G6PD	glucose 6-phosphate dehydrogenase
GABA	γ-aminobutyric acid
GAVE	gastric antral vascular ectasia
GBS	Guillain–Barré syndrome
GCS	Glasgow Coma Scale
G-CSF	granulocyte colony-stimulating factor
GDA	gastroduodenal artery
GH	genetic haemochromatosis
GI	gastrointestinal (*also* glycaemic index)
GIST	gastrointestinal stromal tumours
Glu	glutamic acid
GMC	General Medical Council (UK)
GMP	guanosine monophosphate
GO	gastro-oesophageal
GOJ	gastro-oesophageal junction
GORD	gastro-oesophageal reflux disease
GTN	glyceryl trinitrate
GU	gastric ulcer
GvHD	graft-versus-host disease
GWAS	genome-wide association study
H&E	haematoxylin and eosin
H_2RA	H_2-receptor antagonist
HAART	highly active antiretroviral therapy
HAS	human albumin solution
HAV	hepatitis A virus
Hb	haemoglobin
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B envelope antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDU	high-dependency unit
HDV	hepatitis D virus
HE	hepatic encephalopathy
HELLP	haemolysis–elevated liver enzymes–low platelets (syndrome)
HEV	hepatitis E virus
HGD	high-grade dysplasia
HGV	hepatitis G virus
HHV	human herpes virus
HIDA	hepatobiliary iminodiacetic acid (hepatobiliary scintigraphy)
HII	hepatic iron index
HIV	human immunodeficiency virus
HNIG	human normal immunoglobulin
HNPCC	hereditary non-polyposis colorectal cancer
HOCM	hypertropic obstructive cardiomyopathy
HP	*Helicobacter pylori*
HPF	high-power field
HPV	human papillomavirus
HR	heart rate
HRM	high resolution manometry
HRQL	health-related quality of life
HRS	hepatorenal syndrome
HRT	hormone replacement therapy
HSV	herpes simplex virus
HTLV	human T lymphotropic virus
HUS	haemolytic uraemic syndrome
HV	hepatic vein
HVPG	hepatic venous pressure gradient
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICP	intracranial pressure
IF	intrinsic factor
IFAT	indirect fluorescent antibody test
IFN	interferon
IL	interleukin
IM	intramuscular
INR	international normalized ratio
IPAA	ileal pouch–anal anastomosis
IPMT	intraductal papillary mucinous tumour
IPSID	immunoproliferative small intestinal disease (alpha-chain disease)
IPVD	intrapulmonary vascular dilatation
IRIS	immune reconstitution inflammatory syndrome
ITU	intensive therapy unit
IU	international units
IV	intravenous

IVIG	intravenous immunoglobulins
JVP	jugular venous pressure
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma-associated herpes virus
LARS	laparoscopic anti-reflux surgery
LBx	liver biopsy
LC	laparoscopic cholecystectomy
LCHAD	long-chain 3-hydroxyacyl coenzyme A dehydrogenase
LCT	long-chain triglyceride
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
LGD	low-grade dysplasia
LGV	lymphogranuloma venereum
LH	luteinizing hormone
LIF	left iliac fossa
LKM1	liver–kidney microsomes, type 1
LLQ	left lower quadrant
LMWH	low molecular weight heparin
LOS	lower oesophageal sphincter
LRLT	living-related liver transplant
LS	liver stiffness
LUQ	left upper quadrant
MAC	*Mycobacterium avium complex*
MAHA	microangiopathic haemolytic anaemia
MAI	*Mycobacterium avium intracellulare*
MALT	mucosa-associated lymphoid tissue
MAP	mean arterial pressure
MARS	molecular absorbance recirculation system
MC&S	microscopy, culture and sensitivities
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCN	mucinous cystic neoplasm
MCT	medium-chain triglyceride
MCTD	mixed connective tissue disease
MCV	mean corpuscular volume
MELD	model for end-stage liver disease (score)
MEN	multiple endocrine neoplasia (e.g. MEN-1)
MHA	Mental Health Act
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	myocardial infarction
MIBG	meta-iodobenzylguanidine
MMP	methylmercaptopurine
MMR	measles, mumps, and rubella
Mo	month
MP	mercaptopurine
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSM	men who have sex with men
MSU	mid-stream urine
MTB	*Mycobacterium tuberculosis*
MTTP	microsomal triglyceride transfer protein
NAC	acetylcysteine
NADPH	nicotinamide adenine dinucleotide phosphate (reduced form).
NAFL	non-alcoholic fatty liver
NAFLD	non-alcoholic fatty liver disease
NAPQI	acetyl-p-benzoquinone imine
NASH	non-alcoholic steatohepatitis
NBM	nil by mouth
NBSR	National Bariatric Surgery Registry
NET	neuroendocrine tumours
NF	neurofibromatosis
NG	nasogastric (tube)
NHL	non-Hodgkin's lymphoma
NHS	National Health System (UK)
NICE	National Institute for Health and Care Excellence (UK)
NJ	nasojejunal (tube)
NNT	number needed to treat (for one patient to benefit)
NOGCA	National Oesophago-Gastric Cancer Audit
NRH	nodular regenerative hyperplasia
NSAID	non-steroidal anti-inflammatory drug
NUD	non-ulcer dyspepsia
OATP	organic anion transporting polypeptide
OC	open cholecystectomy
OCA	obeticholic acid

OCP	oral contraceptive pill *or* ova, cysts & parasites
od	once a day
OGD	oesophago-gastro-duodenoscopy
OLT	orthotopic liver transplantation
ORS	oral rehydration solution
PA	postero-anterior *or* pernicious anaemia
PABA	para-aminobenzoic acid
PALS	patient advice and liaison service
PAN	polyarteritis nodosa
PAS	para-aminosalicyclic acid *or* periodic acid–Schiff
PAT	parenteral antischistosomal therapy
PBC	primary biliary cholangitis
PBG	porphobilinogen
PCR	polymerase chain reaction
PCT	porphyria cutanea tarda
PDAI	pouchitis disease activity index
PE	pulmonary embolism
PEG	percutaneous endoscopic gastrostomy *or* polyethylene glycol
PEJ	percutaneous endoscopic jejunostomy
PET	positron emission tomography *or* pancreatic endocrine tumour
PHG	portal hypertensive gastropathy
PICC	peripherally inserted central catheter
PMC	pseudomembranous colitis
PN	parenteral nutrition
PNS	peripheral nervous system
PO	by mouth (*per os*)
POEM	peri-oral endoscopic myotomy
PPI	proton pump inhibitor
ppm	parts per million
PPPD	pylorus-preserving pancreatico-duodenectomy
PR	by (*per*) rectum
prn	as required (*pro re nata*)
PRO	patient-reported outcome
PSA	prostate-specific antigen
PSC	primary sclerosing cholangitis
PT	prothrombin time
PTD	percutaneous transhepatic drainage
PTH	parathyroid hormone
PTLD	post-transplant lymphoproliferative disorder
PUD	peptic ulcer disease
PUO	pyrexia of unknown origin
PV	by (per) vagina
PVT	portal vein thrombosis
qds	four times a day
RA	rheumatoid arthritis
RBC	red blood cell
RCT	randomized controlled trial
RDW	red cell distribution width
RIBA	recombinant immunoblot assay
RIF	right iliac fossa
RIG	radiologically inserted gastrostomy
RUQ	right upper quadrant
SAAG	serum-to-ascites albumin gradient
SAMe	*S*-adenosylmethionine
SBP	spontaneous bacterial peritonitis
SBT	Sengstaken–Blakemore tube
SC	subcutaneous
SCA	sickle cell anaemia
SCC	squamous cell carcinoma
SCFA	short-chain fatty acid
SD	standard deviation
SEDU	specialist eating disorder unit
SeHCaT	selenium-75 labelled homotaurocholic acid test
SEMS	self-expanding mesh metal stent
SIADH	syndrome of inappropriate antidiuretic hormone secretion
siRNA	small interfering ribonucleic acid
SL	sublingual
SLA	soluble liver antigen
SLE	systemic lupus erythematosus
SMA	superior mesenteric artery
SOD	sphincter of Oddi dysfunction
SOM	sphincter of Oddi manometry
SOS	sinusoidal obstruction syndrome
SPECT	single photon emission computed tomography
SRS	somatostatin receptor scintigraphy

SSRI	selective serotonin-reuptake inhibitor
stat	immediately (*statim*)
SVC	superior vena cava
SVR	sustained virological response *or* systemic vascular resistance
TACE	transcatheter chemoembolization
TAE	transanal excision
TB	tuberculosis
TDM	therapeutic drug monitoring
tds	three times a day
TES	transanal endoscopic surgery
TG	triglyceride
TG(N)	thioguanine (nucleotide)
TGF	transforming growth factor
Th1	T helper cell type 1
TIBC	total iron-binding capacity
TIPSS	transjugular intrahepatic portosystemic shunt
TMP-SMX	trimethoprim–sulfamethoxazole (co-trimoxazole)
TNF	tumour necrosis factor
TNM	tumour–node–metastasis (staging system for cancer)
TOF	tracheo-oesophageal fistula
TPMT	thiopurine methyltransferase
TPN	total parenteral nutrition
TSH	thyroid-stimulating hormone
TTS	through-the-scope
U&E	urea and electrolytes
UC	ulcerative colitis
UDCA	ursodeoxycholic acid
UGT	uridine diphosphate glucuronyl transferase
UKELD	UK Model for End-stage Liver Disease
ULN	upper limit of normal
UO	urine output
US	ultrasound
UTI	urinary tract infection
VBL	variceal band ligation
VCE	video capsule endoscopy
VIP	vasoactive intestinal polypeptide
VL	viral load
VOD	veno-occlusive disease
VTEC	verocytotoxin-producing *E. coli*
VZV	varicella zoster virus
WCC	white cell count
WDP	Wilson's disease protein
WE	Wernicke's encephalopathy
WHO	World Health Organization
wk	week
WOPN	walled-off pancreatic necrosis
ZES	Zollinger–Ellison syndrome

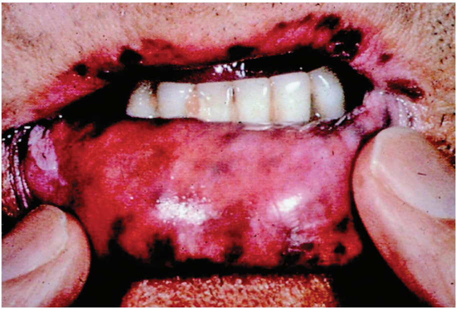

Plate 1 Brown macules on lips in patient with Peutz-Jeghers syndrome

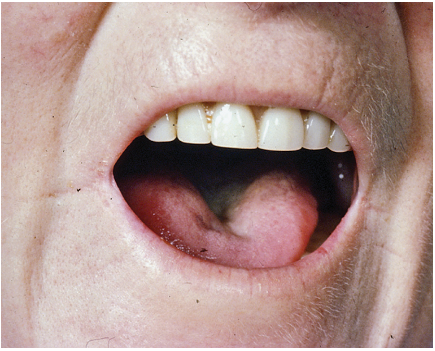

Plate 2 Microstomia due to systemic sclerosis

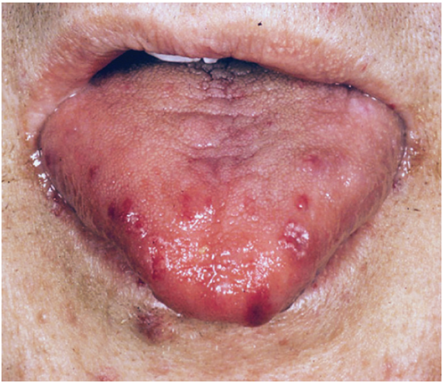

Plate 3 Hereditary haemorrhagic telengiectasia

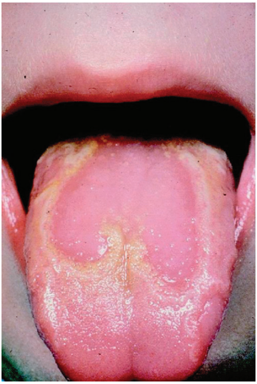

Plate 4 Geographic tongue

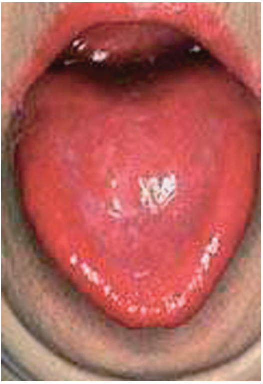

Plate 5 Glossitis

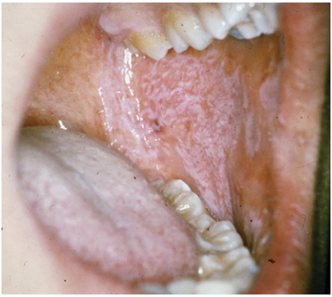

Plate 6 Wickham's striae: associated with lichen planus

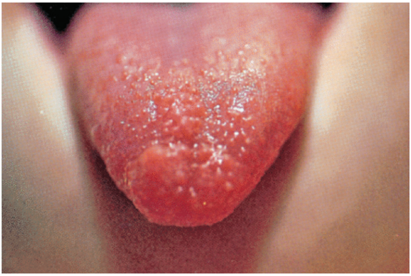

Plate 7 Cowden syndrome, with multiple lingual papillomata

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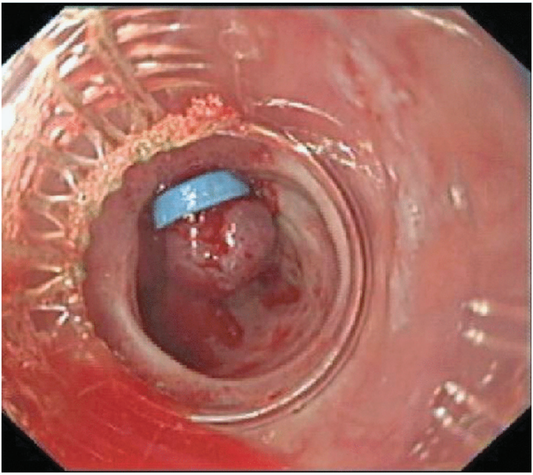

Plate 8 Variceal band ligation

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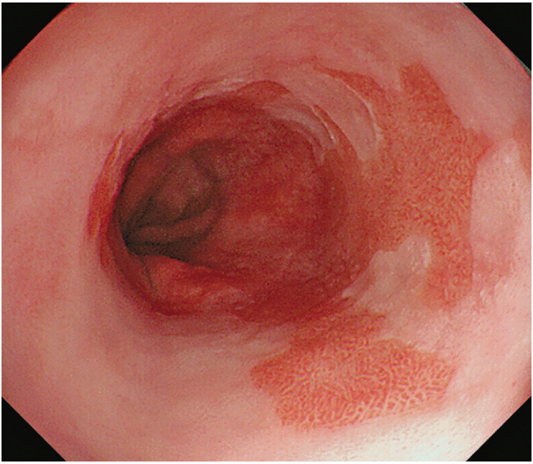

Plate 9 Barrett's oesophagus

Reproduced with permission from Rebecca C. Fitzgerald and Massimiliano di Pietro, *Oxford Textbook of Medicine*, Oxford University Press

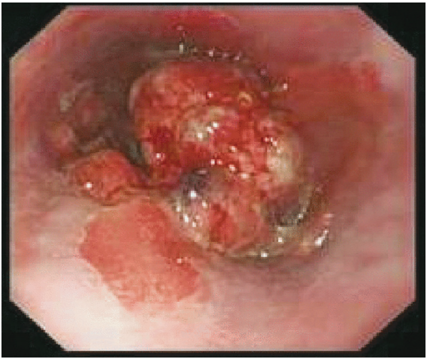

Plate 10 Stenosing oesophageal carcinoma on a background of Barrett's oesophagus

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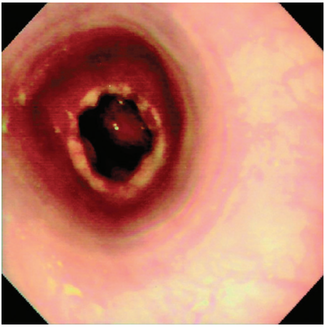

Plate 11 Oesophageal web on endoscopy

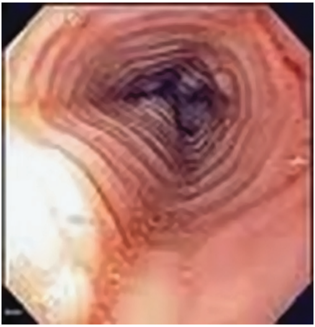

Plate 12 Eosinophilic oesophagitis

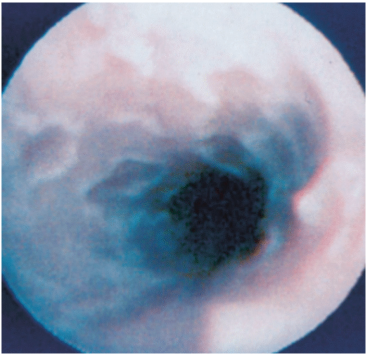

Plate 13 Herpes simplex oesophagitis

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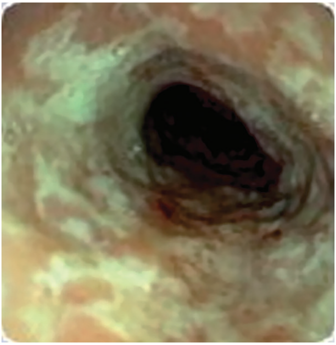

Plate 14 CMV oesophagitis

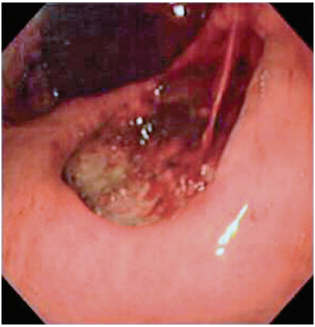

Plate 15 Endoscopic view of bleeding ulcer

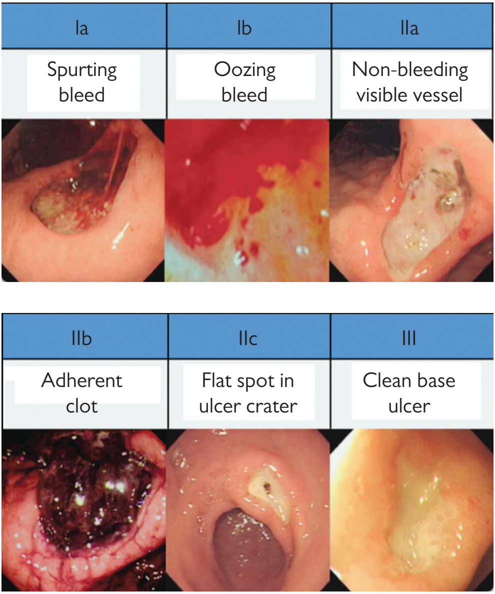
Ia
Spurting bleed
Ib
Oozing bleed
IIa
Non-bleeding visible vessel
IIb
Adherent clot
IIc
Flat spot in ulcer crater
III
Clean base ulcer

Plate 16 Forrest classification

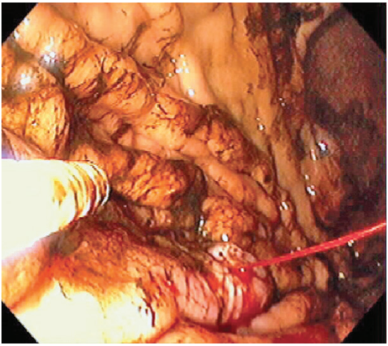

Plate 17 Endoscopic image of spurting Dieulafoy lesion

Reproduced with permission from Klaus Mönkemüller and Walter Curioso, World Gastrointestinal Atlas of Endoscopy (www.giatlas.com)

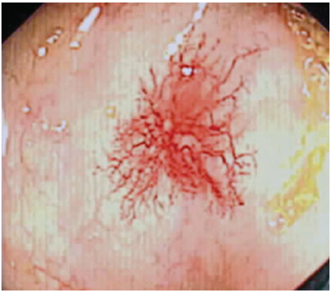

Plate 18 Angiodysplasia

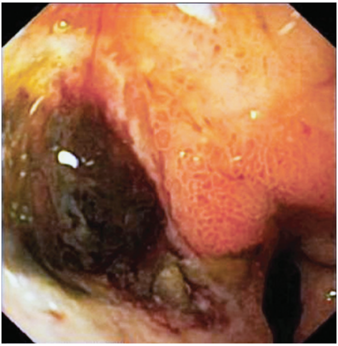

Plate 19 Duodenal ulcer

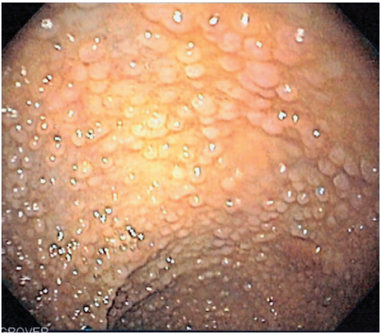

Plate 20 Duodenal familial adenomatous polyposis

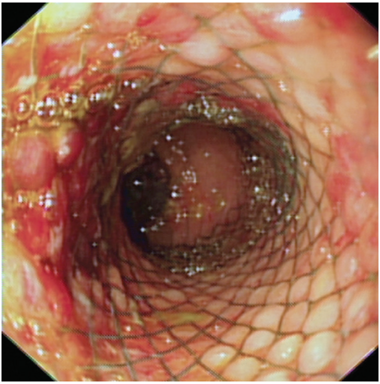

Plate 21 Duodenal mesh metal stent

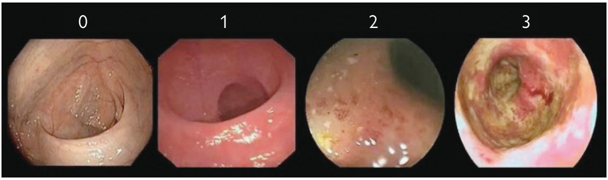

Plate 22 Ulcerative colitis (illustrating the increasing grades of Mayo endoscopic subscore appearances; see Table 4.25)

Reproduced with permission from Samaan, M.A., et al. A Systematic Review of the Measurement of Endoscopic Healing in Ulcerative Colitis Clinical Trials: Recommendations and Implications for Future Research, *Inflammatory Bowel Diseases*, 20:8, 1465–1471, 2014

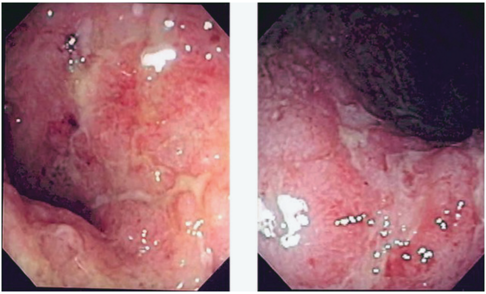

Plate 23 Crohn's disease. Aphthous and serpiginous ulceration

Reproduced with permission from Samaan M.A., D'Haens G. (2015) The Use of Endoscopy to Follow the Clinical Course of Crohn's Disease. In: Kozarek R., Chiorean M., Wallace M. (eds) Endoscopy in Inflammatory Bowel Disease. Springer, Cham

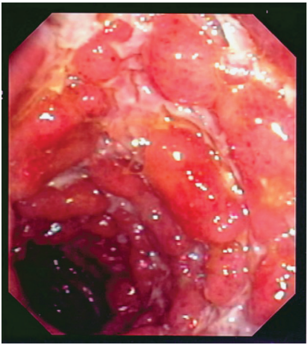

Plate 24 Crohn's disease. Cobblestone appearance of the mucosa

Reproduced with permission from Samaan M.A., D'Haens G. (2015) The Use of Endoscopy to Follow the Clinical Course of Crohn's Disease. In: Kozarek R., Chiorean M., Wallace M. (eds) Endoscopy in Inflammatory Bowel Disease. Springer, Cham

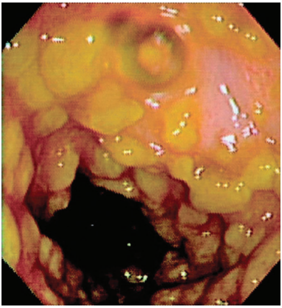

Plate 25 Endoscopic image of pseudomembranous colitis caused by C.*difficile*

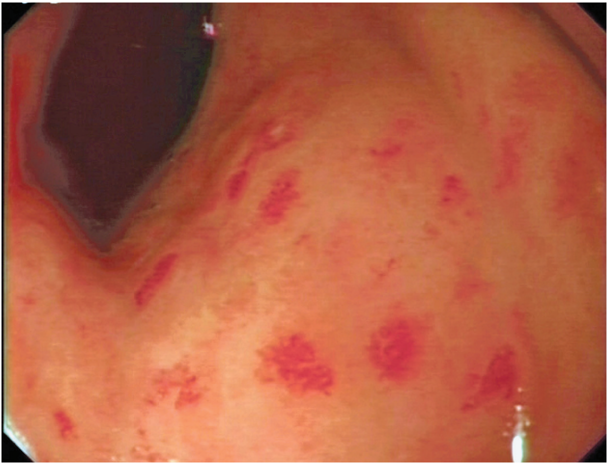

Plate 26 Radiation colitis

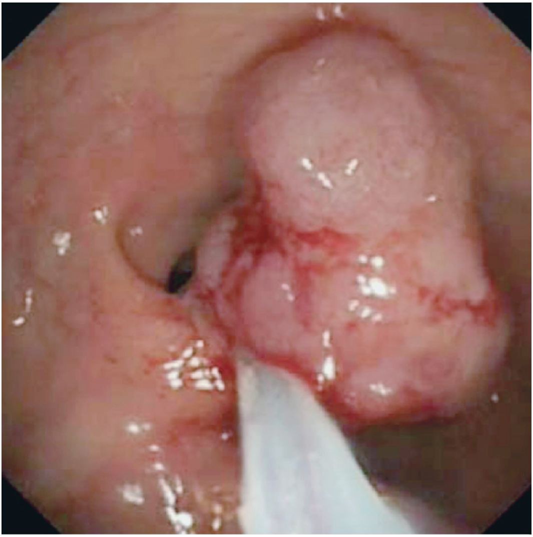

Plate 27 Colonic adenomatous polyp

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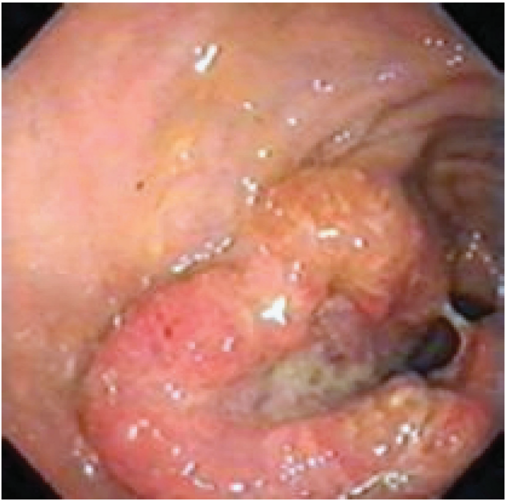

Plate 28 Colon Cancer

Reproduced with permission from Daniel Marks and Marcus Harbord, Emergencies in Gastroenterology and Hepatology, Oxford University Press

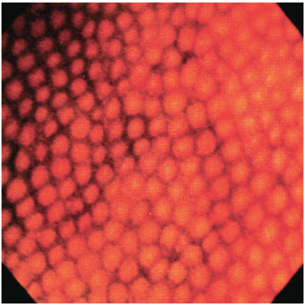

Plate 29 Kudo pit pattern: type 1 (round pits)

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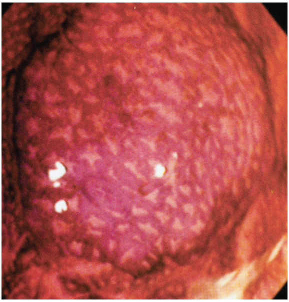

Plate 30 Kudo pit pattern: type 2 (stellar or papillary pits)

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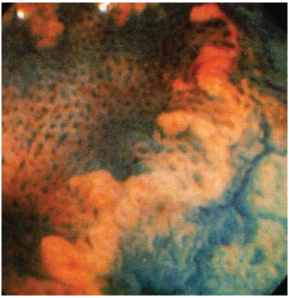

Plate 31 Kudo pit pattern: type 3s (small tubular or roundish pits)

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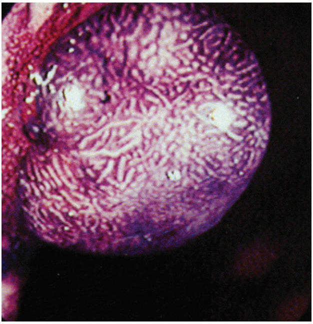

Plate 32 Kudo pit pattern: type 3L (large tubular or roundish pits)

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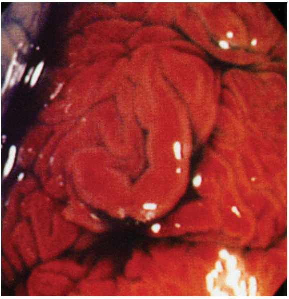

Plate 33 Kudo pit pattern: type 4 (branch-like or gyrus-like pits)

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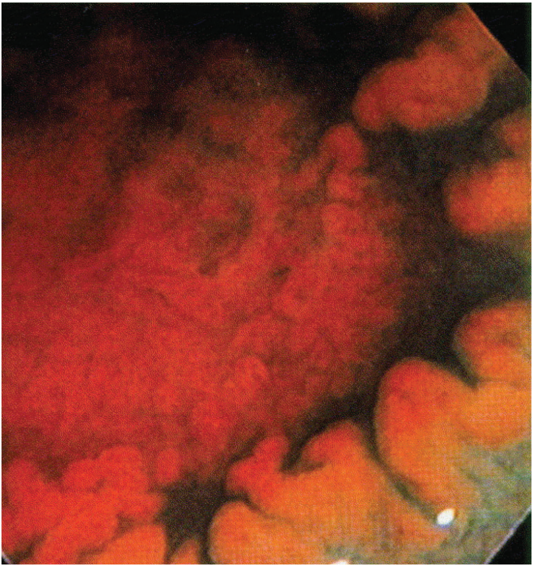

Plate 34 Kudo pit pattern: type 5 (non-structural pits)

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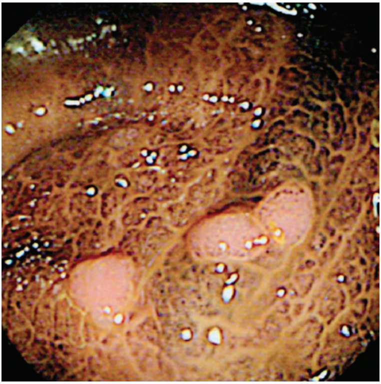

Plate 35 Melanosis coli

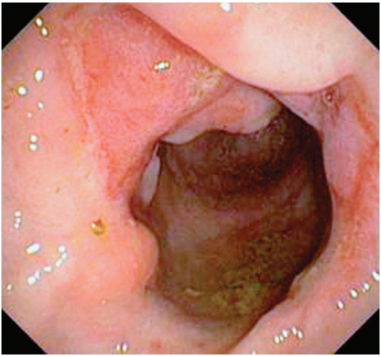

Plate 36 Solitary rectal ulcer

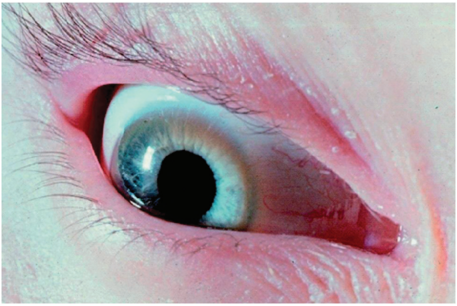

Plate 37 Kayser–Fleischer rings found round the edge of the iris

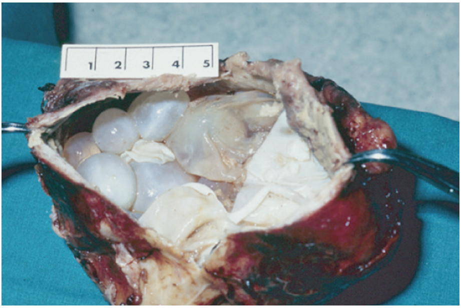

Plate 38 Hydatid cyst. Right hepatectomy specimen showing multiple daughter cysts

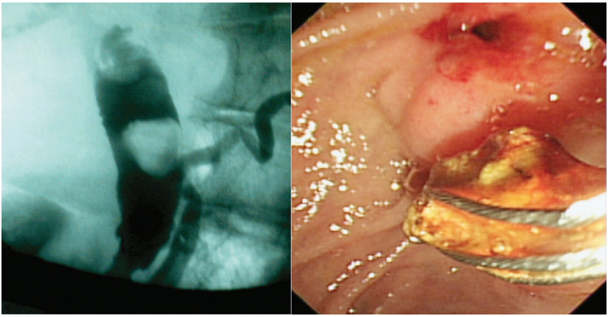

Plate 39 Common bile duct (CBD) stone seen (left) on cholangiogram at ERCP and (right) within the duodenum following removal with an endoscopic basket

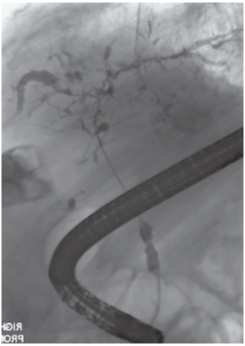

Plate 40 Primary sclerosing cholangitis

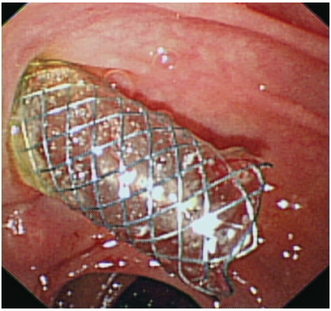

Plate 41 Biliary mesh metal stent

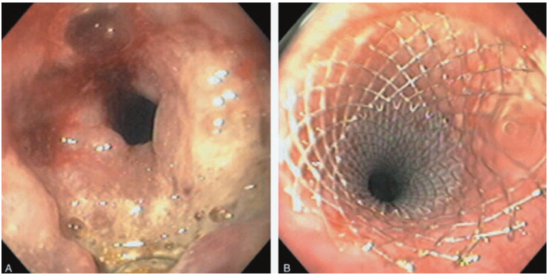

Plate 42 Endoscopically placed biliary and duodenal mesh metal stents in a patient with inoperable pancreatic cancer

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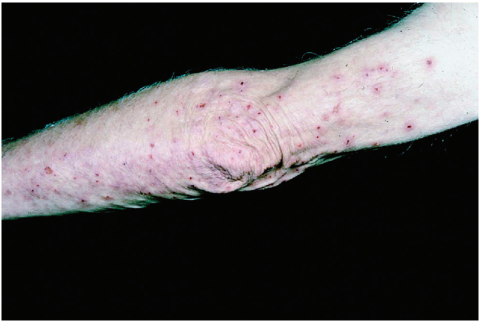

Plate 43 Dermatitis herpetiformis

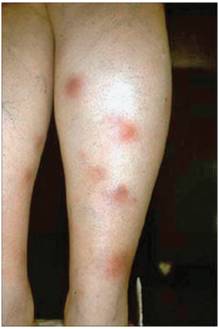

Plate 44 Erythema nodosum

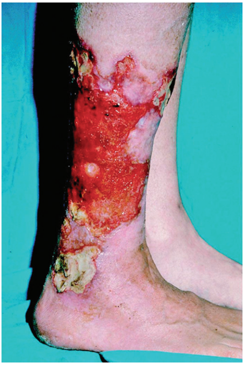

Plate 45 Pyoderma gangrenosum

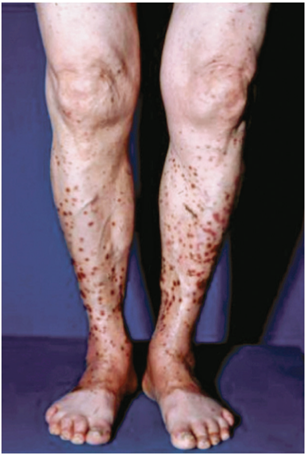

Plate 46 Henoch-Schönlein purpura

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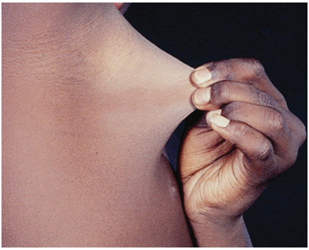


Plate 48 Ehlers Danlos

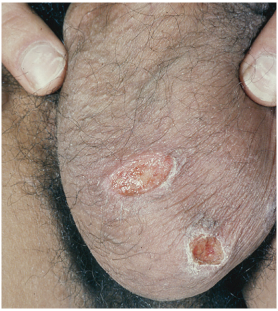


Plate 47 Scrotal ulceration due to Behcet's disease

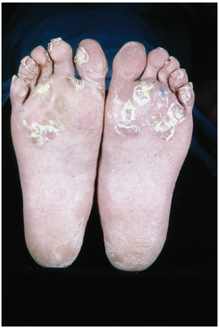


Plate 49 Keratoderma blenorrhagica, often seen as part of Reiters syndrome

Section 1

Approaches to common clinical problems

Acute diarrhoea *2*
Agitation and confusion in the GI patient *8*
Anaemia and occult GI bleeding *10*
Anorectal problems *15*
Ascites *18*
Bloating and wind *22*
Chronic diarrhoea *24*
Chronic or recurrent abdominal pain *33*
Cirrhosis and chronic liver disease *38*
Constipation *42*
Dyspepsia and gastro-oesophageal reflux *50*
Eating disorders *57*
Electrolyte disturbance *64*
Faecal incontinence *73*
Gastrointestinal problems in elderly patients *76*
Gastrointestinal problems in pregnancy *79*
Liver problems in pregnancy *83*
Mouth and swallowing problems *89*
Non-cardiac chest pain *98*
Nutritional support *100*
Obesity *106*
Post-liver transplant patients *108*
Recent-onset jaundice *116*
Unintentional weight loss *121*
Well patients with abnormal liver tests *124*

Acute diarrhoea

Most cases of acute diarrhoea are due to infections and are typically self-limiting, with intervention limited to oral rehydration. Diarrhoea lasting >14d is usually described as persistent (<30d duration) or chronic (>30d), and typically due to other causes (exceptions include ➲ *Giardia* and ➲ *Yersinia*): see ► Approach to chronic diarrhoea.

Key questions in the history

- How long is the history?
- Are there systemic symptoms (fever, tachycardia) or vomiting?
- Is there recognizable blood in the stool?
- How frequent are the stools?
- Presence and location of any associated abdominal pain?
- Any contact with possible infected food or water?
- Recent travel history?
- Any contact with similarly ill people? Anyone in the family unwell?
- On examination, look for signs of dehydration and malnutrition.

Risk factors

- Age. After weaning, the protective effects of breast milk are lost. The elderly may have ↓ immune competence, but also ↓ acid secretion (e.g. due to *Helicobacter* infection, or drugs such as → PPIs).
- Immune deficiency. Includes patients with HIV (see ➲ HIV and the gut), and those on anticancer chemotherapy.
- Medication. See also ➲ antibiotic-associated diarrhoea.
- Travel.
- Infected food and water: either a true infection (with ingestion of enteropathogens that multiply in gut), or ingestion of toxin in food contaminated with enterotoxin-producing microorganism.
- Known sensitivity to certain foods (see ➲ food allergy/intolerance).

Classifying acute diarrhoea

Subdivide according to presence (Box 1.1) or absence (Box 1.2) of blood in stool, since the causes are largely different. Also consider whether the process involves mostly small or large intestine.

Box 1.1 Causes of acute diarrhoea with blood

- ➲ Shigella.
- Enterohaemorrhagic ➲ *E. coli*.
- ➲ *Campylobacter*.
- ➲ *Salmonella.*
- ➲ *Yersinia.*
- ➲ Amoebic dysentery.
- Antibiotic-associated colitis (see ➲ *Clostridioides difficile*).
- ➲ *Schistosoma* (*mansoni*, *intercalatum*, or *japonicum*) or *Tricuris*.
- Diverticulitis.
- Ischaemic colitis.

Box 1.2 Causes of acute diarrhoea without blood

- Viruses (➲ rotavirus, norovirus, astrovirus, ➲ adenovirus, coronavirus).
- Bacteria:
  - Mild infection with ➲ *Shigella*, ➲ *Salmonella*, or ➲ *Campylobacter.*
  - ➲ *E. coli* (enterotoxigenic, enteropathogenic, enteroaggregative).
  - ➲ Cholera, ➲ *Clostridia* species.
- Protozoa: ➲ *Giardia*, cryptosporidiosis, *Cyclospora*.
- ➲ *Strongyloides*.
- Food toxins.
- Malaria.
- Systemic sepsis.
- Toxic shock syndrome.

Pathogens targeting small bowel include toxigenic bacteria, viruses, and *Giardia lamblia* (see ➲ giardiasis). These produce large volume, watery diarrhoea, and mid-abdominal pain. Blood and faecal leucocytes are rare. See Table 1.1.

Pathogens targeting large bowel are usually invasive. They produce lower abdominal or rectal pain, tenesmus, mucoid, or bloody diarrhoea with many faecal leucocytes, and inflamed rectal mucosa. See Table 1.2.

A few pathogens (e.g. ➲ *Salmonella*, ➲ *Yersinia*) infect the lower small bowel but can invade the colon as well. These can present on a spectrum from watery diarrhoea to colitis.

Table 1.1 Infectious agents targeting the small bowel

	Agent	Source and incubation period
Viruses	Rotavirus, norovirus, calcivirus, torovirus, enteric adenovirus	Short incubation (1–3d) for rotavirus and norovirus, longer (8–10d) for adenovirus. Norovirus in shellfish, or acquired in hospitals/care institutions
Bacteria that colonize gut	*Vibrio cholerae*	2–144h. See ➲ cholera
	Vibrio parahaemolyticus	Raw fish or seafood, 2–48h. Usually a short illness
	➲ *Yersinia* ➲ *Salmonella*	Principally invade lower small bowel but may invade colon. Clinical spectrum varies from watery diarrhoea to colitis
	E. *coli* (ETEC, EPEC)	See ➲ *Escherichia coli*
	Giardia	See ➲ giardiasis

Table 1.2 Infectious agents targeting large bowel

➲ *Shigella*	Highly contagious. Spread usually faeco-oral but outbreaks can occur related to contaminated milk, ice-cream, or water. Toxigenic phase of fever, pain and diarrhoea starts early after infection
➲ *Campylobacter*	Incubation period 24–72h. Usual source is infected animals. Most infections result from improperly cooked chicken (50–70% cases)
➲ *Salmonella*	As *Campylobacter*. Toxic megacolon and perforation due to colitis can occur—most common when diarrhoea has lasted 10–15d
E.coli (EIEC, EHEC)	1–14d, mean 3d. See ➲ *Escherichia coli*
Entamoeba histolytica	See ➲ amoebiasis
C. *difficile*	See ➲ clostridial infections in GI tract

Investigations

Most attacks are self-limiting. In general, investigation is indicated in following circumstances:

- Course >2wk.
- Signs of systemic upset, including fever.
- Tenesmus or bloody diarrhoea.

- Special circumstances:
  - Outbreaks suggesting food poisoning.
  - MSM.
  - Immunocompromised host.
  - Ingestion of raw shellfish.
  - Antibiotic usage.

Stool culture is often requested, but few centres test for all pathogens; mixed infections are common, single stool cultures insufficient for some pathogens, and results often come back too late to influence management. In practice, apart from investigation of outbreaks and surveillance, stool culture in uncomplicated cases should be limited to exclusion of those pathogens for which antibiotic treatment is indicated (parasites, *Shigella, V. cholerae*) or where there are other possible causes of acute diarrhoea (e.g. inflammatory bowel disease).

Stool microscopy

- Ova, cysts, and parasites.
- Measurement of faecal leucocytes now rarely performed, or replaced by ▸ faecal calprotectin. Will be positive in ➔ *Shigella*, ➔ *Campylobacter*, and EIEC & EHEC infections; variably so with ➔ *Salmonella*, ➔ *Yersinia*, and *C. difficile*; and negative in ➔ cholera, ETEC/EPEC, viral diarrhoea, and ➔ giardiasis.

Identifying microbial antigens

- ELISA for ➔ *Giardia* is more accurate than stool microscopy and should be ordered when there is an appropriate history.
- Serology/antibody testing are useful for ➔ *Yersinia enterocolitica*.
- ELISA kits are available for ➔ *Strongyloides* and ➔ schistosomiasis.

Imaging

AXR should be taken if patient toxic, to look for evidence of diffuse colitis, ileus, or ➔ toxic megacolon.

Treatment

Fluid replacement

- **Oral rehydration** nearly always preferred route, but if patient vomiting or intravascularly deplete (resting tachycardia with postural hypotension), **IV fluids** may be necessary.
- Unlike situation in patients with intestinal resection or jejunostomy, where sodium concentration of 90–120mM provides maximum salt and water absorption, optimal sodium concentration for rehydration in cases of mild–moderate acute diarrhoea probably ≈50mM. Substitution of starch for rice, or cereal for glucose, associated with less diarrhoea and more rapid resolution.

Diet

Eating during an attack of acute diarrhoea can be uncomfortable because any food provides a stimulus to defaecation. No benefit to fasting, but dairy products should be avoided because of temporary ➲ lactose intolerance. Alcohol, caffeine, and fizzy drinks should be avoided.

Drugs

Antimotility agents can be very useful but should not be used if acute severe colitis because of risk of precipitating ➲ toxic megacolon. → LOPERAMIDE drug of choice.

Indication for antibiotics

- Reasonable to withhold empiric antibiotic therapy in most stable patients pending stool testing. Concerns about precipitating ➲ haemolytic–uraemic syndrome in patients with enterohaemorrhagic ➲ *E. coli*, but given most cases of bloody diarrhoea in adults not due to this pathogen, benefits of empiric treatment in symptomatic adults with severe bloody diarrhoea likely to outweigh risk.
- Community-acquired diarrhoea: >4 stools/d for >3d with ≥1 of pain, fever, vomiting, myalgia, and/or headache. Quinolone such as → CIPROFLOXACIN 250–500mg bd. Optimal duration not known (although 3d suggested), but also single dose given early very effective.
- Traveller's diarrhoea in adults. Duration of diarrhoea ↓ when quinolone such as → CIPROFLOXACIN used.
- Isolation of specific pathogens: ➲ *Shigella*, ➲ *Vibrio cholerae*, ➲ *Salmonella typhi*, ➲ *Clostridioides difficile*. For antibiotic selection for specific organisms, see relevant A-Z entry.
- *Giardia lamblia* (laboratory proven or clinical suspicion high).
- Laboratory-proven enteropathogenic ➲ *E. coli* infection, especially in very young or old. Antibiotic treatment of enterohaemorrhagic *E. coli* of no proven benefit, and theoretical risk of precipitating ➲ haemolytic–uraemic syndrome (HUS).

Diarrhoea in travellers

Around 30–50% of travellers to developing countries have an episode of infective diarrhoea, which is usually mild–moderate in severity and self-limiting. Investigation and treatment may be needed for bloody diarrhoea, when invasive organisms are involved, or when diarrhoea persists for >2wk.

Causal organisms

- Enterotoxigenic ➲ *E. coli* (ETEC) most common cause worldwide (also leading bacterial cause of gastroenteritis on cruise ships), but ➲ *Shigella* accounts for increasing proportion, and ➲ *Campylobacter* important in travellers to Asia.
- Other bacterial pathogens include *Aeromonas*, *Plesiomonas*, and *Vibrio*.
- Viruses (rotavirus, norovirus) responsible for up to 30% of cases.
- Parasitic causes uncommon, but *Giardia* found in 5%. ➲ *Cyclospora* seen occasionally. ➲ *Cryptosporidium* can be problem for immunocompromised.

- Consider ➲ amoebiasis in people with bloody stools.
- Geography affects likely cause. While ETEC and ➲ *Shigella* account for majority of isolates in Africa and Middle East, over 50% of people affected in Asia have ➲ *Campylobacter*.

Natural history, and mode of infection

- Most cases occur 5–15d after arrival. Malaise, anorexia, abdominal cramps, watery diarrhoea, and sometimes nausea with vomiting are hallmarks. Fever in ~50%. Most cases resolve in 6–10d.
- Gastric hypoacidity and immunosuppression ↑ risk, as does ➲ ulcerative colitis, ➲ Crohn's disease, and ➲ coeliac disease.
- Careful selection of food and drink to minimize infection ↓ but does not eliminate risk. Two other approaches are chemoprophylaxis or dispensing medication to be taken if diarrhoea develops.

Chemoprophylaxis

The Center for Disease Control (CDC; Atlanta, USA) does not recommend routine use of prophylactic antibiotics because of concerns about side effects and selection of resistant strains. Two settings where prophylactic antibiotics may be used are:

- Short-term travellers (2wk or less in endemic area) whose business or vacation schedule would be severely disrupted by an episode of diarrhoea.
- Patients with underlying medical conditions or immunocompromise.

Where ETEC, ➲ *Shigella*, or ➲ *Salmonella* predominate, a quinolone (ciprofloxacin 500mg od) is the drug of choice. For travellers to Asia, ➲ *Campylobacter* is common and frequently resistant to quinolones: azithromycin 500mg od should be used.

Self-medication with antibiotics A single dose of → CIPROFLOXACIN 500mg taken at 1st sensation of impending upset can ↓ duration and intensity of infection.

Other aspects of self-treatment Benefit of adding antidiarrhoeal agents such as loperamide (see → ANTIDIARRHOEAL AGENTS) to antibiotics unclear. Very important to ensure adequate fluid and electrolyte replacement using an oral rehydration solution, such as World Health Organization (WHO) rehydration solution.

Diagnostic approach to diarrhoea in the returning traveller

- Initial approach is the same as that for self-treatment of traveller's diarrhoea (3d of quinolone or azithromycin, ± loperamide, and adequate fluid/electrolyte replacement).
- Diarrhoea can be prominent symptom of **malaria**. Examine blood film for *Plasmodium* in travellers returning from malarial areas with fever and diarrhoea.
- Watery diarrhoea persisting >10d most commonly due to ➲ giardiasis. Send stool to be examined for *Giardia*, *Cryptosporidium*, *Cyclospora*, and *Isospora*.
- Empirical treatment with → METRONIDAZOLE or tinidazole for *Giardia* often reasonable. If fails to improve, further investigation with upper GI endoscopy and small bowel biopsy, sigmoidoscopy, and rectal biopsy required. If symptoms and biopsies consistent with ➲ tropical sprue, tetracycline with folic acid indicated.

Agitation and confusion in the GI patient

Background

'Disturbed consciousness' covers a wide range of clinical states, from mild disorientation and agitation, to drowsiness and coma. The midnight call to the ward to see a confused uncooperative 'liver patient' often represents a diagnostic and management challenge. The range of possible causes is wide (Box 1.3), but it is important to make the correct diagnosis, as treatment for one cause may be detrimental to another. Acute confusional states are usually due to organic cause, and rarely because of mental illness.

Box 1.3 Causes of disturbed consciousness in the GI patient

- ▲ **Hepatic encephalopathy** ▲.
- ➲ Alcohol withdrawal/delirium tremens.
- ➲ Wernicke's encephalopathy.
- GI bleed.
- Intracranial bleed (e.g. subdural).
- Seizure or post-ictal state.
- Sepsis.
- Intracranial infection (meningitis, encephalitis, abscess).
- Hypoglycaemia.
- Hyponatraemia.
- Illicit drug use/overdose.
- Hypoxia.
- Hypercapnia.
- Severe acute renal failure.
- Zinc deficiency.

Assessment

History

- Usually from family, friends, and medical and nursing staff.
- Find out about previous episodes of confusion, head injury, and psychiatric disease.
- Is there a history of alcohol excess, and when did patient last drink?
- Examine drug chart—any new sedatives/constipating agents?

Full general and neurological examination essential

- Review observation chart, including temperature. Ensure vital signs stable and airway protected.
- Is patient in pain (agitation is important manifestation of pain in patients with cognitive impairment).

- Specifically look for:
  - Signs of sepsis.
  - Evidence of malnutrition (➔ Wernicke's encephalopathy).
  - Smell breath (for alcohol and foetor hepatis of encephalopathy).
  - Jaundice and signs of chronic liver disease or ➔ portal hypertension (e.g. splenomegaly, ascites).
  - Liver flap (▲ **hepatic encephalopathy** ▲).
  - Needle marks/tracks (drug overdose, sepsis, cerebral abscess).
  - Tremulousness, tachycardia, and sweating may relate to ➔ alcohol withdrawal (?stopped due to admission 48–72h previously).

Immediate investigations

- Finger prick for glucose BM.
- Pulse oximetry.
- Take blood for:
  - FBC, clotting.
  - U&Es, liver function tests (LFTs), CRP, glucose.
  - Ammonia (in patients with known or suspected chronic liver disease). ❗ However, caveats that ammonia levels are often chronically ↑ in patients with liver disease and elevated readings should not deflect from searching for other causes of perturbed consciousness. In addition, normal value does not completely exclude diagnosis of encephalopathy (which is primarily clinical).
- Exclude sepsis (CXR, blood cultures, MSU/CSU, ascitic tap).
- Consider CT brain (especially if head injury or focal neurology).
- Consider blood and urine for alcohol/drug screen.

Management

- If patient agitated or aggressive, remove objects from around the bed with which the patient may harm themselves or others (e.g. glass vases).
- Nurse in a calm quiet environment, with as few people 'coming and going' as possible. Reasonable lighting helpful to ↓ disorientation.
- Give Pabrinex 2 pairs IV/IM tds for 5d if any risk of ➔ Wernicke's encephalopathy.
- Use of midazolam 0.5–5mg PO/IM/IV (slow up-titration) or haloperidol 5–10mg PO/IM may be necessary in agitated patient, but should be avoided in patients with ▲ **hepatic encephalopathy** ▲ or ➔ alcohol withdrawal.
- Specific management depends on likely diagnosis (see ▲ **hepatic encephalopathy** ▲, ➔ alcohol withdrawal, ➔ Wernicke's encephalopathy).

Anaemia and occult GI bleeding

Anaemia (Hb <120g/L in ♀, <130g/L in ♂) is common in GI practice, and a frequent reason for referral to gastroenterologists by other specialists. Often, gastroenterologists are asked for an opinion on the cause of a macrocytic or microcytic anaemia. Careful testing to identify various haematinic deficiencies is crucial (see Box 1.4). A classification of anaemia related to GI disease is shown in Table 1.3.

Table 1.3 Classification of anaemia related to GI disease

Cause	Type of anaemia
GI bleeding	Iron deficiency
↓ Red cell production	Haematinic deficiency: ➲ iron, ➲ vitamin B_{12} or ➲ folic acid (deficiency seen in pregnancy, ↑ cell turnover, inflammation) Marrow failure: aplastic anaemia, red cell aplasia, marrow infiltration
↑ Red cell destruction	Congenital (haemoglobinopathies, hereditary spherocytosis, red cell enzyme defects) Acquired (immune/non-immune)
Abnormal red cell maturation	Sideroblastic anaemia, myelodysplasia
Drug-related anaemia	See text. May be caused by bleeding (antiplatelets, non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants), drug-induced haemolysis, or marrow aplasia (e.g. mesalazine)
Extraintestinal effects of GI disease	Anaemia of chronic disease Liver, renal, endocrine disease

Haematinic deficiency

Most important are **iron, folic acid, and vitamin B_{12}**, but **copper and vitamins A, B_6, C, E, riboflavin, and nicotinic acid** also needed for erythropoiesis. Deficiency can arise through inadequate intake, malabsorption, ↑ need or use, or loss.

Box 1.4 Basic tests for haematinic deficiency

- FBC: Hb, red cell indices (MCV, MCHC, MCH, RDW), WCC and differential, platelets).
- Blood film examination.
- Reticulocyte count, haptoglobin, Coomb's test.
- Iron, total iron binding capacity (TIBC), transferrin saturation, ferritin.
- Vitamin B_{12}, and serum (± red cell) folate.
- U&Es.
- ➤ LFTs including albumin and γGT.

Table 1.4 Causes of common haematinic deficiency in GI disease

	Iron	B_{12}	Folate
Nutritional	Rarely sole cause	Vegans	Poor diet: elderly, alcohol misuse, institutionalized
Malabsorption			
Stomach	Anacidity: ➲ Atrophic gastritis ➤ Gastrectomy	➲ Pernicious anaemia ➲ Atrophic gastritis	➤ Gastrectomy
Small intestine	➲ Coeliac disease ➲ Tropical sprue	➲ Bacterial overgrowth Ileal resection ➲ Crohn's disease ➲ Coeliac disease ➲ Tropical sprue Fish ➲ tapeworm	➤ Gastric bypass ➲ Coeliac disease ➲ Tropical sprue ➲ Systemic sclerosis ➲ Amyloidosis ➲ *Giardia* Diabetic enteropathy ➲ Lymphoma ➲ Whipple's disease
Other		➲ Chronic pancreatitis	Alcohol
Loss or ↑ utilization	Bleeding		Liver disease ➲ Crohn's disease

For details of treatment of haematinic deficiencies and further details of individual causes, see ➲ iron, ➲ vitamin B_{12}, and ➲ folic acid.

Increased red cell destruction: haemolysis

Red cell destruction is mainly extravascular in liver, spleen, and bone marrow. Haem is metabolized to bilirubin, conjugated in liver, and excreted in faeces and urine.

Congenital causes

- Unconjugated hyperbilirubinaemia due to excess haemolysis seen in neonate as result of:
  - **Congenital spherocytosis** (in adult, spherocytosis usually indicates antibody-mediated red cell destruction), or
  - **Non-spherocytotic causes** such as inherited red cell enzyme defects (e.g. G6PD deficiency).
- **Haemoglobinopathies** These include structural haemoglobin variants such as ➲ sickle cell disease and disorders of globin chain synthesis (➲ thalassaemias).

Acquired causes

- In adults can be seen in severe liver disease due to abnormal lipid composition of red cells.
- Disseminated cancers (e.g. arising from gastric or pancreatic primary) can cause disseminated intravascular coagulation and micro-angiopathic haemolytic anaemia (see Tables 1.4 and 1.5).

Diagnosis

Plasma haptoglobins bind to haemoglobin and are ↓ in intravascular haemolysis and in liver disease. Coomb's test will confirm autoimmune-mediated haemolysis. Haemolysis can result in pigment ➲ gallstones, which can be presenting feature of illness.

Drug-related anaemia

Think of the following:

- Upper GI irritation causing blood loss: → NSAIDs, aspirin. Combination of → NSAIDs and → CORTICOSTEROIDS associated with high risk of upper GI bleeding.
- Bleeding due to or exacerbated by specific drugs, e.g. clopidogrel, warfarin, heparin, direct oral anticoagulants (e.g. dabigatran, rivaroxaban, apixaban).
- Drug-induced haemolysis, e.g. oxidative haemolysis due to sulfasalazine, dapsone, or ribavirin.
- Production impairment (e.g. aplasia secondary to mesalazine).

Anaemia in liver disease

Table 1.5 Causes of anaemia in liver disease

Cause	Comment
Dilutional	↑ Plasma volume, splenomegaly.
Iron deficiency	Bleeding. Iron status can be difficult to establish. Ferritin may be ↑ as an acute phase protein. Transferrin, accounting for much of TIBC, often ↓. MCV may be normal or ↑ due to concomitant effects of chronic alcohol use or folate deficiency.
Vitamin B_{12} and folate	Liver stores B_{12} and folate. Folate often deficient in alcohol misuse due to poor nutrition and effect of alcohol in ↓ folate absorption.
Haemolysis	May be autoimmune in association with ➲ autoimmune hepatitis. Red cell lifespan ↓ due to abnormal membrane—if severe can produce 'spur cell' anaemia. Alcohol can cause sideroblastic anaemia. Haemolysis seen in ➲ Wilson's disease (probably due to copper toxicity to red cells). ➲ Zieve's syndrome.
Aplastic anaemia	Viral hepatitis: parvovirus, ➲ hepatitis A, B, C, EBV, CMV. Hepatitis often mild and marrow aplasia severe: damage may be immune-mediated. Alcohol may have direct marrow toxicity effects.

Iron-deficiency anaemia presumed to be due to occult GI blood loss

This is a common situation in gastroenterological practice, and a common reason for referral by non-gastroenterologists. Up to 100ml blood loss/d can still result in grossly normal looking stools. The source of bleeding is unidentified in ~5% of patients with GI bleeding.

▹ Faecal occult blood testing can be helpful, particularly if menorrhagia is suspected as a cause of anaemia in menstruating ♀. Iron deficiency diagnosed by either ↓ ferritin or ↓ transferrin saturation (ratio of ➲ iron to TIBC). Beware missing iron deficiency because of normal TIBC: this reflects mostly transferrin synthesis by liver, which can be impaired in chronic disease or inflammation.

Diagnosing the cause of iron-deficiency anaemia

History

- Focus on drugs that injure GI mucosa (e.g. aspirin, NSAIDs, bisphosphonates, potassium salts).
- Take a careful family history for bleeding disorders (e.g. unexpectedly heavy bleeding after relatively minor procedures, such as dental extractions).

Examination

Look for cutaneous stigmata of systemic diseases (➲ dermatitis herpetiformis, neurofibromas, lip freckles suggestive of ➲ Peutz–Jeghers syndrome (Plate 1), mucosal telangiectasia in ➲ hereditary haemorrhagic telangiectasia (Plate 3), osteomas suggestive of ➲ Gardner's syndrome).

Investigations

Initial assessment may direct investigations to particular part of GI tract. For example:

- Dyspepsia or a clear history of NSAID or other irritant drug ingestion directs need for upper GI endoscopy, and a positive family history of ➲ colon cancer, change of bowel habit, or iron deficiency in elderly patient with aortic stenosis (suggesting possibility of ➲ angiodysplasia) will necessitate colonoscopy.
- In absence of clear symptoms, upper GI endoscopy and colonoscopy at same session improves cost-effectiveness and results in significantly ↑ diagnostic yield over either investigation alone.
- CT colonography appropriate where colonoscopy contraindicated. Sensitivity >90% for lesions >10mm.
- Screen for ➲ coeliac disease by testing serology, but if not performed, consider duodenal biopsy at the time of endoscopy.

Investigation of the patient with suspected occult GI bleeding or definite blood loss but normal upper GI endoscopy/colonoscopy

This is influenced by the briskness of bleeding.

- If there is any suggestion of an upper GI lesion, repeat upper GI endoscopy by a senior endoscopist using an enteroscope or paediatric colonoscope identifies lesions in substantial proportion of patients.
- Further imaging is probably not necessary in most patients unless there is inadequate response to iron therapy.
- In patients with inadequate response, ➤ video capsule endoscopy (VCE) or ➤ enteroscopy can detect lesions such as ➲ angiodysplasia, ➲ Crohn's disease, or small bowel neoplasia. VCE has a diagnostic yield of ≈50%. Any symptom of intestinal obstruction or suggestion of luminal narrowing should prompt initial evaluation with a gelatine 'patency capsule', safe passage of which does much to minimize risks of impaction of the video capsule.
- In those with active bleeding, CT angiography can localize site of haemorrhage, but requires bleeding rate of ≥2ml/min. Can be followed by direct selective angiography for therapeutic embolization. Scintigraphy with ^{99}Tc-labelled RBCs now rarely performed.
- ➤ Double balloon enteroscopy permits visual inspection of the whole GI tract, along with diagnostic biopsy and therapeutic intervention, but involved procedure and not available everywhere.
- ➲ Meckel's scans may be helpful if no other bleeding source found.

Guidelines

BSG guidelines for the management of iron deficiency anaemia (2011). 🖱 http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/sbn/bsg_ida_2011.pdf.

Anorectal problems

Anal discomfort or pain and passage of bright red blood from the anus are common symptoms, often reported with some embarrassment and anxiety by patients. Many are frightened by thought of an anorectal examination. A definite diagnosis, with clear explanation of condition and available therapies, will make future visits less of an ordeal.

Clinical assessment

- Any bleeding must be carefully defined: spots of fresh blood on the paper suggest a perianal source, while darker blood or blood mixed in with stool suggest pathology higher up the colon.
- In cases of perianal pain, sepsis should always be looked for, but this can be difficult to detect in the clinic.
- Rigid sigmoidoscopy is frequently unsatisfactory, and now usually not done in clinic; ➢ flexible sigmoidoscopy is preferable. ➢ Endoanal US, ➢ examination under anaesthetic, and ➢ MRI are useful ancillary investigations.

Anal lesions

- Bleeding or prolapse of tissue through the anus is a common presentation of ➲ haemorrhoids. Diagnosis can be made on proctoscopy.
- Anal skin tags, fibroepithelial polyps, and thrombosed external piles are all relatively minor conditions that can cause major symptoms. Referral to a surgeon for excision may be needed.
- ➲ Rectal prolapse can be mistaken for prolapsing haemorrhoids. Diagnosis can usually be made by examining patient straining to pass stool. Unpleasant as it sounds, it is best to examine the patient sitting on lavatory rather than in left lateral position.
- ➲ Anal fissures can cause agonizing pain. May be diagnosed on history with careful examination of the anal canal, but sometimes examination under anaesthetic is needed. Treatment now often medical (e.g. with topical GTN or diltiazem ointment) rather than traditional lateral sphincterotomy or the discredited anal stretch. See ➲ anal fissure for details of medical management.
- ➲ Anorectal abscesses usually result from infection of anal glands along the dentate line. Acute infection may cause abscess and lead to chronic fistula. Abscess classified according to extent, and may be perianal, ischiorectal, intersphincteric, or supralevator. Causes and important differential diagnoses shown in Table 1.6.

Table 1.6 Causes and differential diagnosis of anorectal fistulae

Causes of anorectal fistulae	➲ Crohn's disease, trauma, ➲ TB, foreign bodies, anal surgery
Differential diagnosis	Pilonidal sinus, hidradenitis suppurativa, carcinoma, Bartholin's abscess, lymphoma

- While perianal abscess may be easy to diagnose, ischiorectal abscess can be much less obvious. Sepsis higher up the anal canal can present as rectal pain. Abscesses may communicate with anorectum: this may present as a fistulous tract.
- Assessing ➲ anorectal fistulae traditionally involves examination under anaesthetic, but MRI and EUS have role in defining anatomy. Any discharging area or granulation tissue around anus should be assumed to communicate with anorectum until proven otherwise.
- Perianal itching (➲ pruritus ani: most common site for intractable itch in the body). Many causes. Often managed by patients with variety of creams and lotions. Rarely help, and may make itching worse.
- Frequency of ➲ perianal Crohn's disease varies from ≈15% in association with small bowel disease, to ≈35% in patients with ileocolitis or colitis alone. While management of associated sepsis may involve surgery or radiologically guided drainage, conservative approach is usually indicated and medical management often provides best chance of healing, especially with → anti-TNF monoclonal antibodies. Other medical approaches include antibiotics (→ METRONIDAZOLE, → CIPROFLOXACIN), and → AZATHIOPRINE.
- Sexually transmitted diseases (see Table 1.7).

Table 1.7 Sexually transmitted diseases with anorectal manifestations

Organism	Condition
Human papilloma virus	Perianal warts (condylomata accuminata)
➲ Herpes simplex virus	Vesicles can occur around anus or in anal canal
Treponema pallidum (syphilis)	Primary or secondary lesions
Chlamydia	Can cause proctitis or even stricturing
Gonococcus	Can be asymptomatic

Rectal lesions

- Rectal discomfort or dissatisfaction, and passage of blood per rectum, are the most common symptoms of rectal disease. Digital examination and proctoscopy or sigmoidoscopy should allow exclusion of ➔ rectal cancer, inflammation, or ➔ solitary rectal ulcer. ➔ Rectal prolapse diagnosed from history and examining patient straining to pass stool.
- Outpatient rigid sigmoidoscopy often gives very limited views and most clinicians proceed straight to flexible sigmoidoscopy to define cause of rectal bleeding.
- Investigation of rectal discomfort may involve defaecating proctogram (see ➢ defaecography studies) to define mechanical problems with defaecation or ➔ rectocoele. Endoanal US or pelvic MRI best tools to define perianal anatomy.
- Injury to anorectum from radiation therapy important cause of symptoms: up to 20% of patients receiving pelvic radiotherapy suffer radiation proctitis (see ➔ radiation injury to the GI tract).

Ascites

Intraperitoneal accumulation of fluid. Range of causes (see Table 1.8). In resource-rich countries, ➲ portal hypertension due to cirrhosis accounts for 80%, with intra-abdominal malignancy and heart failure making up most of rest. Note that ascites rarely occurs due to ➲ portal vein thrombosis in isolation, but may develop in setting of systemic sepsis or low serum albumin.

Table 1.8 Causes of fluid within the peritoneal cavity (i.e. ascites)

Mechanism	Causes
➲ Portal hypertension	Parenchymal liver disease (e.g. ➲ cirrhosis, ➲ alcoholic hepatitis, ▲ **acute liver failure** ▲), right heart failure, constrictive pericarditis, ➲ sinusoidal obstruction syndrome, ➲ Budd–Chiari syndrome, ➲ portal vein thrombosis
Peritoneal inflammation	➲ Spontaneous bacterial peritonitis, malignant peritoneal deposits, ➲ TB, connective tissue disease (e.g. ➲ SLE, ➲ sarcoidosis, ➲ familial Mediterranean fever)
↓ Plasma oncotic pressure	Hypoalbuminaemic states (e.g. nephrotic syndrome, severe malnutrition, ➲ protein-losing enteropathy)
Impaired lymphatic drainage	Lymphatic obstruction (e.g. right heart failure, ➲ TB, lymphoproliferative disorders), lymphatic tear (e.g. trauma)
Other	Hypothyroidism, pancreatic ascites (ruptured pseudocyst or disrupted main duct)

Assessment of ascites

Always consider

- Is there unequivocal evidence of ascites (hospital admission and intensive investigation of portal hypertension rarely effective treatment for central obesity!)?
- What is the cause of ascites?
- What is the optimal management?

History

Full history essential, especially in those with recent-onset ascites. Focus on:

- Symptoms and risk factors for cirrhosis (see ► Approach to cirrhosis and chronic liver disease), ➲ portal hypertension, and cardiac disease.
- Internal malignancy (including recent weight loss and RUQ discomfort in cirrhotics, suggestive of ➲ hepatocellular carcinoma).
- Sepsis (including abdominal ➲ TB and ➲ spontaneous bacterial peritonitis).

Examination

Look for signs of:

- Chronic liver disease (see ► Approach to GI examination), ▲ **hepatic encephalopathy** ▲ (e.g. jaundice, liver flap).
- ➲ Portal hypertension: splenomegaly, dilated abdominal veins, caput medusa (superficial veins radiating out from umbilicus). Ascites due to portal hypertension usually occur in setting of hyperdynamic circulation (↑ HR, vasodilatation, ↓ mean arterial BP).
- Cardiac failure (cardiomegaly, ↑ JVP).

Investigation

- Bloods: FBC, U&Es, LFTs, ESR, CRP, clotting. Full assessment of causes of liver disease as appropriate (see ► Approach to recent-onset jaundice). Consider amylase (pancreatitis) and brain natriuretic peptide (heart failure), depending on suspected cause.
- Imaging. ▷ US and Doppler or contrast ▷ CT allow portal vein flow to be assessed, as well as intra-abdominal organs. 'Internal echoes' or 'septae' within ascites may suggest infection.
- Diagnostic ascitic tap essential in all cases, including in patients with known cirrhosis and ascites in hospital (who have high rate of ➲ spontaneous bacterial peritonitis. See ▷ paracentesis. 20ml of fluid should be drawn, and assessed for:
  - **Colour** (see Fig. 1.1) Usually straw coloured. Blood suggests 'blood tap' or malignancy; white/milky suggests chylous ascites.
  - **White cell count** Normal <500 white cells/μl, <250 neutrophils/μl.
  - **Ascitic albumin** Allows calculation of serum-to-ascites albumin gradient (SAAG), which accurately differentiates ascites due to ➲ portal hypertension (SAAG >11g/L) from non-portal hypertension in >97% of cases.
  - **Microscopy and culture** Always inoculate into blood culture bottles. AFB positive in fluid of <20% of cases of peritoneal TB.
  - **Cytology** In suspected malignancy, providing larger volumes of fluid to the cytopathologist (e.g. >100ml) increases yield.
- Urinalysis (& 24h urine collection) if proteinuria.
- Further investigations tailored to results and clinical picture (e.g. ECG, CXR, echocardiogram if possible heart failure). Ascitic amylase >2,000IU/L suggests pancreatic ascites (e.g. following ➲ pancreatic pseudocyst rupture), and ascitic bilirubin > serum bilirubin supports diagnosis of biliary leak (e.g. ▷ post-cholecystectomy). Chylous ascites diagnosed by ascitic triglyceride (TG) level of >110mg/dl (and always with ascitic TG > plasma TG).

See Fig. 1.1 for diagnosis based on ascitic fluid analysis.

Management

Vital to treat underlying cause, not just manage ascites (see ➢ Approach to cirrhosis and chronic liver disease).

Portal hypertensive ascites

- **Salt restriction** No added salt to food should be specified, and a low-salt diet is preferable, but patient compliance with <1.5g/d (60mmol/d) is poor. However, salt restriction alone may lead to resolution of ascites in 20% of patients.
- **Restriction of fluid** to 1.5L is a standard component of management, but as fluid loss in ascites directly related to negative Na^+ balance, fluid restriction rarely effective in absence of salt restriction.
- **Diuretics** A combination of spironolactone and furosemide usually required. Commence spironolactone 100mg/d and furosemide 40mg/d. Increase dosages every 4–5d to maximum spironolactone 400mg/d and furosemide 160mg/d, titrated against body weight (aim ↓0.5kg/d). Monitor U&Es for renal impairment, hyponatraemia and hyper/hypokalaemia.
- This approach does not work in 10%, defined as 'refractory ascites'. Treatment options then include large volume therapeutic ➢ paracentesis, surgical shunting, ➲ transjugular intrahepatic portosystemic shunt (TIPSS), or ➲ liver transplantation.
- Surgical portosystemic shunts and peritoneovenous shunts now rarely used as high complication rate and availability of alternatives.
- TIPSS effective at controlling ascites in most patients, but high occlusion rate (30–50% at 1y) and risk of ▲ **hepatic encephalopathy** ▲ (up to 30%), particularly in those with poor liver synthetic function (i.e. ↑ Bn, ↑ INR, ↓ serum albumin).
- ➲ Liver transplantation is definitive treatment for cirrhotic ascites, in patients who have 5y survival of 20% with medical therapy alone.

Non-portal hypertensive ascites

- Malignant ascites is usually refractory to diuretics, and requires repeated therapeutic ➢ paracentesis. Generally very poor prognosis.
- Biliary peritonitis requires endoscopic or percutaneous biliary stenting & surgery, depending on cause.
- Similarly, management of pancreatic ascites depends on exact site and cause of pancreatic leak, with approaches including pancreatic rest (e.g. with NJ feeding), percutaneous drainage, endoscopic ➲ pancreatic stent insertion, ➢ EUS-guided pancreatic pseudocyst drainage, surgical pancreatic resection (e.g. ➢ Whipple's procedure or distal pancreatectomy), or → OCTREOTIDE (can ↓ pancreatic fluid output). Assess and manage in specialist centre.
- Tuberculous ascites treated with appropriate anti-TB therapy.
- Long-term tunnelled ascitic drains may be appropriate in palliative cases to avoid repeated hospital admission.

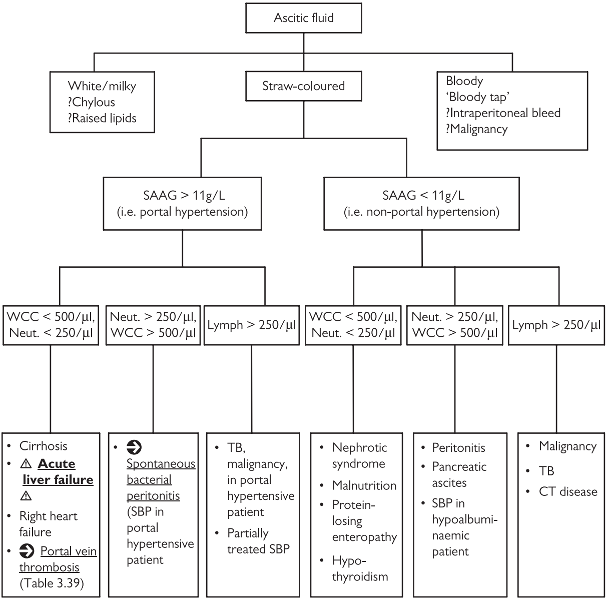

Ascitic fluid
White/milky
?Chylous
?Raised lipids
Straw-coloured
Bloody
'Bloody tap'
?Intraperitoneal bleed
?Malignancy
SAAG > 11g/L
(i.e. portal hypertension)
SAAG < 11g/L
(i.e. non-portal hypertension)
WCC < 500/µl, Neut. < 250/µl
Neut. > 250/µl, WCC > 500/µl
Lymph > 250/µl
WCC < 500/µl, Neut. < 250/µl
Neut. > 250/µl, WCC > 500/µl
Lymph > 250/µl
Cirrhosis
⚠ Acute liver failure ⚠
Right heart failure
➜ Portal vein thrombosis (Table 3.39)
➜ Spontaneous bacterial peritonitis (SBP in portal hypertensive patient
TB, malignancy, in portal hypertensive patient
Partially treated SBP
Nephrotic syndrome
Malnutrition
Protein-losing enteropathy
Hypo-thyroidism
Peritonitis
Pancreatic ascites
SBP in hypoalbumi-naemic patient
Malignancy
TB
CT disease

Fig. 1.1 Diagnosis of cause of ascites using SAAG and cell count. Although SAAG strongly predicts whether ascites is due to portal hypertension, interpretation of WCC necessitates incorporation of clinical information and other results (e.g. culture, cytology).

Bloating and wind

Excessive gas production is a common symptom causing patients to seek advice. Patients may attribute abdominal cramps, bloating, chest discomfort, audible bowel sounds, belching, and flatulence to gaseousness.

Composition and volume of intestinal gas

Main gases in flatus are oxygen and nitrogen (which come largely from swallowed air), and hydrogen, methane, and carbon dioxide (which come from intestinal lumen). Hydrogen and methane are largely products of bacterial metabolism; carbon dioxide can be derived from bacterial fermentation of dietary substances.

Excretion of flatus averages 600ml/d, and is no greater in patients complaining of gaseousness, suggesting heightened sensitivity to intestinal stretch or abnormal motility rather than ↑ volume, similar to observations in patients with ➲ irritable bowel syndrome.

Clinical assessment

History and examination

See Box 1.5.

Investigation

- FBC, U&Es, LFTs. Consider screening for ➲ coeliac and ➲ *Giardia* if history suggestive. Small intestinal ➲ bacterial overgrowth can be indicated by malabsorption of vitamins B_{12} and D.
- Any blood in stool should prompt investigation of colon.
- Plain AXR.
- Consider upper and lower GI contrast examinations to exclude intestinal obstruction.

Therapy

- Air swallowing is common: reassurance and stopping gum chewing and smoking (including electronic cigarettes) can help.
- Belching often results from discomfort due to gastro-oesophageal reflux: acid suppression can be helpful.
- ➲ Bacterial overgrowth may contribute and need treating.
- Excessive flatus may respond to dietary modification (↓ intake of legumes, beans, fruits, and complex carbohydrates).
- Activated charcoal, taken orally before a meal, can ↓ breath hydrogen.

- Some patients may have delayed intestinal transit and be constipated. Treatment with ↑ dietary fibre or non-stimulant osmotic laxatives (not lactulose, which is fermented in gut) can relieve constipation, but may initially cause ↑ bloating. Preliminary evidence that some probiotic bacteria (*Bifidobacter infantis*, present in VSL-3) may alleviate bloating in ➔ irritable bowel syndrome.

Box 1.5 Assessment of the gaseous patient

History

- **Diet** Legumes, beans, apples, prunes, raisins, and starches can all ferment, resulting in gas production.
- **Medications** Narcotics, analgesics, calcium channel blockers.
- **Surgery** 25–50% of patients experience gas bloating after Nissen fundoplication.
- **Psychiatric factors** such as anxiety or depression can be relevant.
- **Systemic diseases** ➔ Diabetes (gastroparesis due to autonomic neuropathy), ➔ systemic sclerosis (altered motility due to neuromuscular dysfunction), neuromuscular disorders such as muscular dystrophy, hypothyroidism.

Physical examination

- Examine for signs of weight loss, ascites, air swallowing, anxiety, and peritonitis. Look for succussion splash.

Chronic diarrhoea

Definition

Defined as diarrhoea >30d duration (if <14d, see ► Approach to acute diarrhoea). Patient's perception of diarrhoea needs to be clarified (↑ looseness of stools, ↑ frequency of stools, urgency, abdominal discomfort, faecal incontinence). Stool weight (>235g/d in ♂, >175g/d in ♀) has been used to define diarrhoea, but weighing stool unpleasant and disliked by patient, nurse, and laboratory, and in any case stool weight >ULN with normal consistency is not necessarily diarrhoea. Working definition of chronic diarrhoea is persistent abnormal passage of ≥3 loose stools/d.

Classification into **watery diarrhoea** (osmotic or secretory), **fatty diarrhoea** (steatorrhoea), or **inflammatory diarrhoea** is useful, but there may be considerable pathophysiological overlap. Investigation of steatorrhoea is described further in ► Approach to malabsorption and steatorrhoea.

Pathophysiology and causes

Osmotic

Occurs due to presence in the gut of excess poorly absorbable, osmotically active solutes. Stool water content directly relates to faecal output of solutes exerting osmotic pressure across intestinal mucosa (electrolyte composition may vary according to electrical charge on poorly absorbed anions or cations, which is why measuring stool electrolytes is rarely useful). This explains two clinical hallmarks of osmotic diarrhoea:

- Diarrhoea stops when the patient fasts, or at least stops eating the poorly absorbed solute causing diarrhoea.
- Stool analysis, if necessary, will reveal an osmotic gap. That is, $\{2 \times [Na^+] + [K^+]\}$ (to account for anions) is < faecal osmolality (usually assumed to be isotonic to plasma, i.e. 290mOsm/kg).

Secretory

Results from abnormal ion transport by intestinal epithelial cells. Four main categories of disease may be involved:

- Congenital defect in ion absorption.
- Intestinal resection.
- Diffuse mucosal disease, damaging/reducing epithelial cell numbers.
- Abnormal mediators (including neurotransmitters, bacterial toxins, hormones, and cathartics) that affect intestinal chloride and water secretion through changes in intracellular AMP and GMP.

Secretory diarrhoea is characterized by two features:

- Stool osmolality accounted for by Na^+ + K^+, and related anions, so the osmotic gap is small.
- Diarrhoea usually persists during a 48–72h fast.

Inflammatory (exudative)

Inflammation and ulceration may lead to loss of mucus, proteins, pus, or blood into bowel lumen. Diarrhoea accompanying intestinal inflammation may be due to impairment of normal colonic absorptive function.

Altered motility

Little experimental proof exists that ↑ motility causes diarrhoea, but has been implicated in:

- Diarrhoea of ➲ irritable bowel syndrome.
- Post-gastrectomy diarrhoea.
- ➲ Diabetic diarrhoea.
- ➲ Bile acid malabsorption-induced diarrhoea.
- Diarrhoea associated with hyperthyroidism.
- Drug-related diarrhoea (e.g. erythromycin as a motilin agonist, nicotine in electronic cigarettes).

Box 1.6 Causes of osmotic diarrhoea

Carbohydrate malabsorption

- Congenital:
  - Specific (disaccharidase deficiency, glucose–galactose malabsorption, fructose malabsorption).
  - Generalized (➲ abetalipoproteinaemia, congenital ➲ lymphangiectasia, enterokinase deficiency, ➲ pancreatic insufficiency (e.g. due to ➲ cystic fibrosis)).
- Acquired:
  - Specific (e.g. post-enteritis disaccharidase deficiency).
  - Generalized malabsorption—see ► Approach to malabsorption and steatorrhoea (➲ pancreatic insufficiency/biliary obstruction, ➲ bacterial overgrowth, ➲ coeliac disease, parasitic disease, ➲ short bowel syndromes, mucosal damage or disease, post-mucosal obstruction in lymphangiectasia, previous surgery including gastrectomy or intestinal resection leading to ➲ bile acid malabsorption).

Excess ingestion of poorly absorbed carbohydrate

- Lactulose therapy, sorbitol in elixirs or 'sugar-free' sweets, fructose in soft drinks or dried fruits, mannitol in sugar-free products, excess bran, or fibre.
- Magnesium-induced diarrhoea from antacids and laxatives.
- Laxatives containing poorly absorbed anions such as sodium sulphate, phosphate, or citrate.

Functional (IBS)

- Consider food hypersensitivity.

Box 1.7 Causes of secretory diarrhoea

- **Congenital** (microvillus inclusion disease, absent Cl/HCO_3 exchanger).
- **Acquired:**
    - Bacterial enterotoxins: ➲ cholera, ETEC, ➲ *Campylobacter*, ➲ *Clostridium*, *S. aureus*).
    - Hormones: VIPoma, medullary carcinoma of thyroid (calcitonin, prostaglandins), ➲ gastrinoma, villous adenoma, small bowel ➲ lymphoma.
    - Stimulant laxatives: phenolphthalein, anthraquinones, castor oil, cascara, senna.
    - Other drugs: antibiotics, diuretics, theophyllines, thyroxine, anticholinesterases, colchicine, prokinetics, ACE inhibitors, antidepressants (SSRIs), prostaglandins, gold.
    - Toxins: plants and fungi (*Amanita*), organophosphates.
    - Food products: caffeine, monosodium glutamate.

Box 1.8 Causes of inflammatory diarrhoea

- Infection: bacterial, viral, parasitic.
- Inflammatory bowel disease: ➲ ulcerative colitis, ➲ Crohn's disease, ulcerative jejunoileitis, ➲ microscopic colitis (often related to NSAIDs).
- Cytostatic agents: chemotherapy, radiotherapy.
- Hypersensitivity: ➲ eosinophilic gastroenteritis, nematodes, ➲ food allergy.
- Autoimmune: ➲ graft versus-host disease.
- ➲ Diverticular disease/diverticular colitis.
- Ischaemia.
- Radiation.
- Neoplasia (➲ colonic cancer, ➲ lymphoma).

Note: some causes of diarrhoea do not fit easily into this classification, e.g. ischaemic colitis (see ➲ intestinal ischaemia), ➲ amyloidosis).

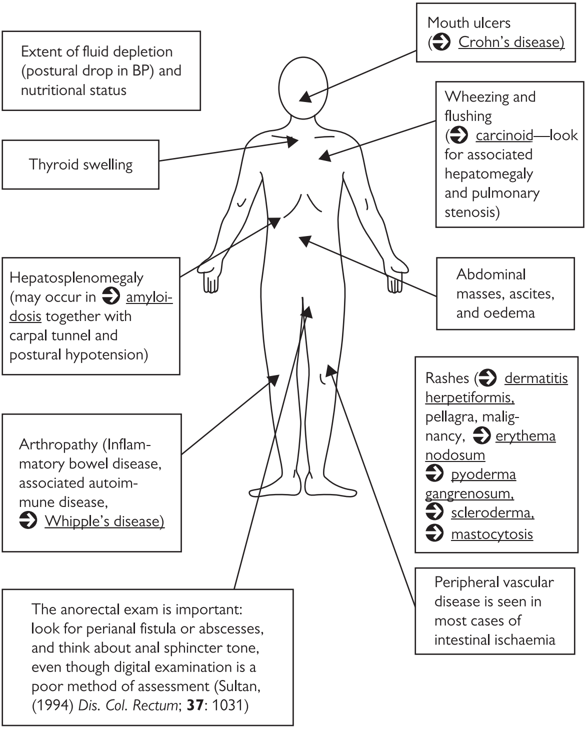
History and examination (Fig. 1.2)

Taking a history of diarrhoea

- Clarify what the patient means by diarrhoea, and if acute or chronic.
- Aims of history are to:
    - Distinguish organic (e.g. duration <3mo, weight loss, nocturnal symptoms, continuous symptoms) from functional causes (absence of organic symptoms + long history and positive symptoms as defined by Rome criteria—see ➲ irritable bowel syndrome).
    - Distinguish malabsorptive diarrhoea (bulky, malodorous, difficult to flush, pale stools) from other causes (liquid/loose stools with blood or mucus).

Stool character and associated symptoms

- Consistently large volume diarrhoea likely to come from small bowel or proximal colon.
- Bloody diarrhoea indicates infectious, neoplastic, or inflammatory process; accompanying lethargy or anorexia may suggest mucosal cytokine release.
- Pale floating stools suggest steatorrhoea and is commonly due to pancreatic insufficiency (stools float because of gas content due to carbohydrate fermentation, not fat).



Extent of fluid depletion (postural drop in BP) and nutritional status

Thyroid swelling

Hepatosplenomegaly (may occur in ➔ amyloidosis together with carpal tunnel and postural hypotension)

Arthropathy (Inflammatory bowel disease, associated autoimmune disease, ➔ Whipple's disease)

The anorectal exam is important: look for perianal fistula or abscesses, and think about anal sphincter tone, even though digital examination is a poor method of assessment (Sultan, (1994) *Dis. Col. Rectum*; **37**: 1031)

Mouth ulcers (➔ Crohn's disease)

Wheezing and flushing (➔ carcinoid—look for associated hepatomegaly and pulmonary stenosis)

Abdominal masses, ascites, and oedema

Rashes (➔ dermatitis herpetiformis, pellagra, malignancy, ➔ erythema nodosum ➔ pyoderma gangrenosum, ➔ scleroderma, ➔ mastocytosis

Peripheral vascular disease is seen in most cases of intestinal ischaemia

Fig. 1.2 Examining the patient with diarrhoea.

Assess for specific causes of diarrhoea

- Family history of inflammatory bowel disease, ➲ coeliac disease, ➲ colon cancer.
- Previous GI surgery leading to ↑ transit, ➲ bacterial overgrowth, or ➲ bile salt malabsorption.
- Systemic disease such as ➲ diabetes mellitus, thyroid disease (heat intolerance and palpitations may suggest hyperthyroidism), ➲ carcinoid (with associated flushing), ➲ systemic sclerosis.
- Drugs. See lists in text and Boxes 1.6–1.8—alcohol, caffeine, and non-absorbable carbohydrates such as sorbitol often missed. Don't forget surreptitious laxative abuse—factitious diarrhoea occurs in 4% of cases in general hospitals, but up to 20% in tertiary referral units.
- Foreign travel, exposure to contaminated water or potential pathogens (e.g. ➲ *Salmonella* in food handlers, *Brucella* on farms).
- Evidence of ➲ chronic pancreatitis.
- Sexual history is important. Anal intercourse is a risk factor for proctitis (causes include gonococcus, ➲ *herpes simplex*, *chlamydia*, ➲ amoebiasis), and oroanal transmission of ➲ *giardia*.
- Always ask about ➲ faecal incontinence: common (2% of population) and not always reported spontaneously. If present, take obstetric history in ♀ for perineal trauma and possible sphincter damage.
- Ask about diet and stress as aggravating factors. There is a link between physical/sexual abuse and functional bowel disease.
- Ask about illness in companions or family members.

Likely causes of diarrhoea in common clinical categories

- **Acute diarrhoea** See ▶ Approach to acute diarrhoea).
- **Chronic/recurrent diarrhoea, not previously investigated:**
  - ➲ Irritable bowel syndrome.
  - Inflammatory bowel disease (IBD): ➲ Crohn's disease, ➲ ulcerative colitis.
  - Parasitic or fungal infection.
  - Malabsorption.
  - Drugs or food additives.
  - ➲ Colonic cancer.
  - ➲ Diverticular disease.
  - Previous surgery.
  - Endocrine causes (e.g. thyroid disease).
  - Faecal impaction.
- **Chronic diarrhoea in previously investigated patients:**
  - Surreptitious ➲ laxative abuse.
  - ➲ Faecal incontinence.
  - ➲ Microscopic colitis.
  - Unrecognized malabsorption.
  - ➲ Neuroendocrine tumours.
  - ➲ Food allergy.

- **Nosocomial (hospital-acquired) diarrhoea** Diarrhoea is among the most common nosocomial illnesses (occurs in 30–50% of patients on ITU), and ⅓ patients in chronic care facilities have at least 1 significant diarrhoeal illness/y. Two classes of patients need particular consideration.
  - **Diarrhoea in patients on ITU** Drugs, especially those containing magnesium and sorbitol, ➔ antibiotic-associated diarrhoea (➔ *C. difficile*, but also ↓ salvage of carbohydrate by colonic bacteria leading to osmotic diarrhoea), enteral feeding, intestinal ischaemia, pseudo-obstruction, faecal impaction, defective anal continence.
  - **Patients with cancer or on chemotherapy** Incidence of GI toxicity with chemotherapy or radiotherapy can approach 100% with some regimens. Radiation enterocolitis occurs at total body doses of ≥6Gy or pelvic irradiation of 3–4Gy (see ➔ radiation damage and the GI tract). Toxic chemotherapeutic agents include cytosine, daunorubicin, 5FU, methotrexate, 6-MP, irinotecan, and cisplatin. Some biological treatments (e.g. anti-IL-2 therapy) associated with watery diarrhoea, and the newer checkpoint inhibitors (e.g. anti-PD-1) can cause autoimmune colitis. ➔ Typhlitis (neutropenic enterocolitis) also potent cause of diarrhoea.
- **Diarrhoea in HIV-infected patients** *Cryptosporidium, Microsporidia, Isospora*, ➔ amoebiasis, ➔ *Giardia*, herpes, ➔ CMV, ➔ adenovirus, MAI, ➔ *Salmonella*, ➔ *Campylobacter*, *Cryptococcus, Histoplasma, Candida*, ➔ lymphoma, AIDS enteropathy (see ➔ HIV and the gut).
- **Diarrhoea in HIV-negative MSM** ➔ Amoebiasis, ➔ giardiasis, ➔ *Shigella*, ➔ *Campylobacter*, syphilis, gonorrhoea, *Chlamydia*, herpes simplex.

Diagnostic tests

Do not accept diagnosis of diarrhoea without some attempt to examine stool, even if only on glove after rectal exam, to look for blood, mucus, oil, or steatorrhoea.

- 75% of chronic diarrhoeas can be diagnosed by careful history and examination, coupled with basic haematology and biochemical tests, stool testing for infection and ⊳ faecal calprotectin, and sigmoidoscopy with biopsy.
- In remainder, consider three further tests to get to definitive diagnosis:
  - Colonoscopy with biopsies.
  - Faecal elastase or quantitative stool fat.
  - Stool volume and osmotic gap in response to fasting.
- Indicators of functional rather than organic aetiology are long history (>1y), lack of significant weight loss, absence of nocturnal diarrhoea, and straining with defaecation. These indicators, taken together, ≈70% specific for functional symptoms.

Basic investigations

- Send three stool samples for:
    - **Culture.** Including ova, cysts, and parasites. Also consider testing for ➲ *C. difficile* if risk factors.
    - ➢ **Faecal calprotectin.** Alternatives depending on availability are faecal lactoferrin or ➢ stool microscopy for faecal leucocytes. If present, suggests inflammatory diarrhoea.
    - Toxicology. If you suspect factitious diarrhoea or laxative abuse, send stool and urine for laxative screen.
- **Blood tests** FBC, ESR, CRP, iron, B_{12}, folate, thyroid function, glucose, U&Es, calcium, LFTs including albumin, coeliac serology.
- In most cases of diarrhoea where histology helps to make diagnosis, **sigmoidoscopy** is sufficient rather than full colonoscopy. The exception is when ileal histology is needed, or changes are patchy throughout the colon. Where there is significant weight loss or bleeding to suggest lower GI malignancy, full **colonoscopy** is needed.
- **Radiological imaging** Plain AXR can show faecal impaction, pancreatic calcification, intestinal dilatation, or suggest colitis.

Stool fat

Historically a very useful test for fat malabsorption, but now often difficult to get done at all (many labs will refuse sample). Can be assessed qualitatively or quantitatively (see ➢ 'Stool tests', p. 151), and if the latter, >7g/d is abnormal. Largely replaced for assessment of pancreatic exocrine insufficiency by measurement of ➢ faecal elastase.

Response to fasting and stool osmotic gap

Rarely of practical use in most cases, but may be useful in difficult cases.

- Steatorrhoeic stools are usually >700g/24h, and stool weight returns to normal on fasting. Inflammatory diarrhoeas respond variably to fasting but, like steatorrhoea, the stool osmotic gap is not usually helpful.
- Measuring stool electrolytes and osmotic gap may help classify chronic watery diarrhoeas. Analysis done on centrifuged sample, so results are possible from spot stool samples or 24–72h collections.
- Assume faecal osmolality = plasma (290mOsm/kg). This is true of freshly passed stool, but with time measured faecal osmolality can become falsely ↑ due to bacterial degradation of carbohydrate. Large measured deviations below 290mOsm/kg indicate contamination of stool with urine or water, gastrocolic fistula, or hypotonic fluid intake. In principle, stool sodium/potassium is high in secretory diarrhoea (unabsorbed electrolytes retain water in gut lumen) and low in osmotic diarrhoea (non-electrolytes retain water in gut lumen). Interpretation of stool osmotic gap and faecal electrolytes is shown in Table 1.9.

Table 1.9 Stool osmotic gap* and faecal electrolytes in the investigation of diarrhoea

Stool Na >90mM and osmotic gap <50mM	Secretory diarrhoea, or osmotic diarrhoea caused by sodium sulphate or phosphate ingestion
Stool Na <60 and osmotic gap >125mOsm/kg	Osmotic diarrhoea: if stool volume does not return to normal on fasting, suspect surreptitious magnesium ingestion
Stool Na >150 and stool osmolality >375–400mOsm/kg	Suspect contamination with urine
Stool osmolality <200–250mOsm/kg	Suspect contamination of stool with dilute urine or water

* Stool osmotic gap = plasma osmolality (~290mOsm/kg) – 2 × (stool $[Na]^+$ + stool $[K^+]$)

Other tests used in investigating diarrhoea

Specific tests for malabsorption (See also ► Approach to malabsorption and steatorrhoea.)

- *Small bowel biopsy* Duodenal biopsy, which may be combined with small bowel aspirate for microbiological analysis, useful in diagnosing ➲ Crohn's disease (especially in children), ➲ coeliac disease, ➲ Whipple's disease, ➲ giardiasis, ➲ lymphoma, ➲ eosinophlic gastroenteritis, ➲ amyloidosis, ➲ systemic mastocytosis, ➲ lymphangiectasia, and various parasitic and fungal infections.
- *Small bowel imaging* Useful for fistulae, strictures, and previously undetected surgical bypasses.
- ▷ Pancreatic function tests.
- ▷ Breath tests for fat, carbohydrate, and ➲ bacterial overgrowth.
- SeHCAT test (see ➲ bile acid malabsorption).

Specific tests for watery diarrhoea

- Blood levels of certain hormones produced by ➲ neuroendocrine tumours such as gastrin, VIP, somatostatin, pancreatic polypeptide, calcitonin, and glucagon may be useful. See ➢ gut hormone profile.
- Urine levels of 5-HIAA can help diagnose ➲ carcinoid.

Specific tests for inflammatory diarrhoeas

- ➢ Faecal calprotectin usually raised.
- In addition to upper and lower GI endoscopy and small bowel studies, PET-MRI or ➢ indium-labelled leucocyte scanning may be useful, particularly in children.

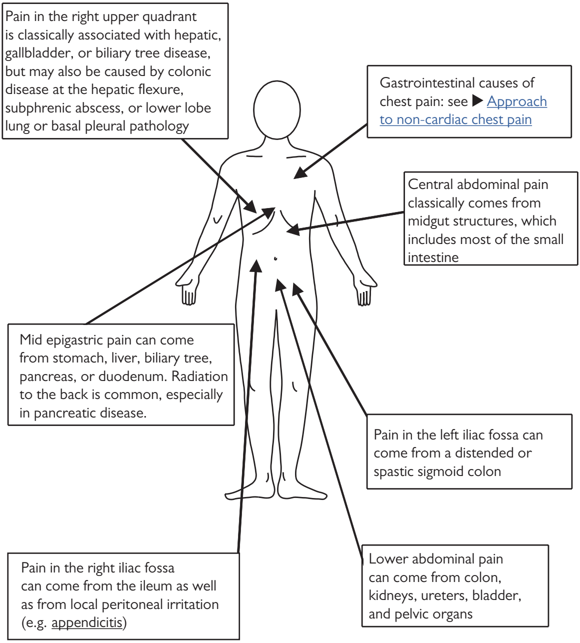
Antidiarrhoeal therapies

These can be divided into agents useful for mild-to-moderate diarrhoeas, and those for secretory or severe diarrhoeas. Most in current use work by ↓ motility rather than secretion. See → ANTIDIARRHOEAL AGENTS.

Chronic or recurrent abdominal pain

Abdominal pain is a very common cause of patients presenting to doctors. **Acute abdominal pain** usually has an organic cause and is dealt with elsewhere (see ▲ **Acute abdominal pain** ▲). While there are many pathological causes of **chronic abdominal pain**, it is commonly not due to organic disease and can thus be a source of worry, frustration, and confusion—to both doctor and patient alike. Diagnosis depends on interpreting the patient's experience into a medical model of disease. This can be difficult because of:

- The common innervation of many abdominal organs.
- The low concentration of nerve endings in the viscera.
- Patients' lack of prior experience of pain coming from these organs.
- The non-specific nature of the pain.



Pain in the right upper quadrant is classically associated with hepatic, gallbladder, or biliary tree disease, but may also be caused by colonic disease at the hepatic flexure, subphrenic abscess, or lower lobe lung or basal pleural pathology

Gastrointestinal causes of chest pain: see ▶ Approach to non-cardiac chest pain

Central abdominal pain classically comes from midgut structures, which includes most of the small intestine

Mid epigastric pain can come from stomach, liver, biliary tree, pancreas, or duodenum. Radiation to the back is common, especially in pancreatic disease.

Pain in the left iliac fossa can come from a distended or spastic sigmoid colon

Pain in the right iliac fossa can come from the ileum as well as from local peritoneal irritation (e.g. appendicitis)

Lower abdominal pain can come from colon, kidneys, ureters, bladder, and pelvic organs

RUQ and LUQ pain can be attributed to lung or pleural pathology.

Fig. 1.3 Clinical approach to chronic or recurrent abdominal pain.

Types of abdominal pain

Distinguish between **visceral** pain (originates from noxious stimuli affecting abdominal viscus, and usually felt in midline); **parietal or somatic** pain (arising from stimulation of parietal peritoneum, usually localized to site of lesion); **referred** pain (felt in remote areas supplied by same neurosegment as diseased organ because of shared central pathways for afferent neurons from different sites); and **non-visceral** pain**.**

Critical features in assessing pain

- Site of pain, and where it radiates to (see Fig. 1.3).
- **Nature** of the pain. Ulcers 'gnaw', viscera 'colic', and ruptured aneurysms 'tear'. Long duration of pain tends to correlate with non-organic cause, especially if not associated with weight loss (see ► Approach to unintentional weight loss) or other alarm symptoms. Estimating severity of pain is very unreliable.
- **Factors modifying pain** can be very helpful in diagnosis.
  - Aggravating foods, or more usually relationship of pain to eating, may be helpful. Alcohol can aggravate dyspepsia and intestinal spasm, cause pancreatitis, or worsen lymphoma pain.
  - Relief by bowel action or passing flatus suggests colonic source (see ➔ irritable bowel syndrome).
  - Pain related to menstruation suggests ➔ endometriosis or pelvic inflammatory disease.

Physical examination

- **Tachycardia, fever, and sweating** suggest infection, although can be absent in chronic infection. Frequent changes of position suggest visceral pain with no or little inflammation.
- **Inspect** For scars, hernias, and visible peristalsis.
- **Palpate** Rigidity or guarding suggests local peritonism. Palpable mass may result from organ enlargement, inflammation, or tumours.
- **Percussion** Tympany suggests excess air, either intraluminal or extraluminal. Light percussion, if painful, can suggest peritonism. Shifting dullness suggests ascites.
- **Auscultation** may reveal tinkling bowel sounds in intestinal obstruction, absent bowel sounds in ➔ ileus, or bruits.
- Do rectal (PR) and, if necessary, vaginal (PV) examinations. Clear prior discussion of need for internal examination vital, and presence of chaperone important. Tenderness on PR or PV examination may not be appreciated by examining anterior abdominal wall.

Investigations

- FBC with MCV (iron studies, B_{12}, and folate if this is abnormal, or within normal range with ↑ RDW), ESR, and CRP.
- Check renal function and ➢ LFTs.

- Examine urine for pyuria and haematuria, and send sample for MC&S. If appropriate, check ♀ of childbearing age for pregnancy.
- *Do not* use inappropriate radiological tests. ⊳ Abdominal US can be highly informative and is non-invasive.
- Other tests depend on results of history and examination.

Non-visceral abdominal pain

When patients present with persistent or recurrent pain, it can be easy to overlook a non-visceral source. This may result in multiple unnecessary investigations, or application of a 'functional' or 'psychosomatic' label (with treatment directed accordingly). Pain may derive from:

- *Abdominal wall*:
  - Comprised of fat, aponeurosis, musculature, and skin. Somatic nerve supply from intercostal nerves T7–T12. Patients may have difficulty describing their pain clearly, as accuracy of cutaneous sensation ↓ through deeper tissues.
  - **Carnett's sign** may be helpful. Examine patient supine and identify site of maximum tenderness with examining finger. Ask patient to fold arms across chest and sit halfway up. If continued palpation at same point elicits similar or ↑ pain, this implies abdominal wall pathology. Myofascial trigger points also suggest musculoskeletal pathology.
  - Pain from shingles typically dermatomal and can precede rash.
- *Nerve entrapment*:
  - Rectus abdominis nerve entrapment syndrome causes point tenderness over the linea semilunaris of the rectus sheath.
  - Ilioinguinal or iliohypogastric nerve entrapment cause burning sensation in iliac fossa radiating to groin, with associated hyperaesthesia and/or paraesthesia, generally made worse on movement (although hip flexion often provides some relief). Nerve at risk during appendicectomy, hernia repair, and Pfannensteil incisions.
- *Postoperative incisional pain*.
- *Skeletal pain*:
  - Painful rib syndrome characterized by sharp pains followed by dull ache in lower costal margin, associated with ↑ mobility of anterior costal cartilages of 8th–11th ribs.
  - Precordial catch syndrome affects young patients, who experience abrupt sharp, stabbing chest pain, causing them to catch their breath.

Functional abdominal pain

Functional abdominal disorders account for ≈50% of all patients with abdominal pain seen by doctors, and almost all cases with abdominal pain lasting years. In most cases, diagnosis of ➲ irritable bowel syndrome is possible from history (see Boxes 1.9 and 1.10). A small minority have intractable chronic pain; this may be associated with previous physical or sexual abuse, and onset may coincide with a bereavement.

Box 1.9 Rome IV criteria for irritable bowel syndrome

Recurrent abdominal pain on average at least 1d/wk in last 3mo associated with two or more of the following features:

- Related to defaecation.
- Associated with change in stool frequency.
- Associated with change in form (consistency) of stool.
- Symptoms must have started at least 6mo ago.

Symptoms supporting diagnosis of IBS:

- Abnormal stool frequency.
- Abnormal stool form.
- Difficulties in evacuation.
- Passage of mucus.
- Bloating or feelings of distension.

Box 1.10 Causes of chronic or recurrent abdominal pain

Generalized parietal pain due to peritonitis

- Bacterial peritonitis (including ➲ spontaneous bacterial peritonitis).
- Ruptured cyst.
- ➲ Familial Mediterranean fever.

Localized peritoneal pain

- ➲ Appendicitis, ➲ cholecystitis, ➲ Crohn's disease, ➲ endometriosis, chronic pelvic inflammation.
- Infiltration due to abdominal neoplasms.

Pain from increased tension in viscera

- ▲ **Bowel obstruction** ▲.
- Biliary obstruction (➲ choledocholithiasis).
- Ureteric obstruction.

Ischaemia

- ➲ Intestinal ischaemia (stenosis, embolism, vasculitis).
- ➲ Henoch–Schönlein purpura.

Retroperitoneal causes

- ➲ Chronic pancreatitis.

Extra-abdominal

- Neurological (neurogenic tumours, spinal degenerative disease, herpes zoster).
- Metabolic (diabetic ketoacidosis, Addisonian crisis, acute intermittent ➲ porphyria).
- Haematological (➲ sickle cell anaemia).
- Toxic (lead).

Functional causes

- ➲ Irritable bowel syndrome.
- Non-ulcer dyspepsia.
- Biliary pain (➲ sphincter of Oddi dysfunction).

Overinvestigation can result from lack of clinical knowledge or experience, or failure to spend time taking adequate history. This tends to sustain the disorder, as the patient recognizes the failure of the doctor to grasp the problem, and becomes increasingly frustrated by a succession of normal results. Time, if necessary spread over several visits, may have to be spent exploring emotional factors. A general approach outlined in Box 1.11.

Box 1.11 General approach to patient with functional abdominal pain

Establish rapport and trust Acknowledge symptoms as real and maintain non-judgemental attitude. Schedule brief but frequent appointments, and reassure when needed. Avoid temptation to do more diagnostic tests.

Set appropriate goals Do not expect cure: focus on adjustment, improvement in function, coping, and adaptation. Allow for setbacks.

Consider specialized referrals

- Pain clinic, relaxation training, clinical psychology, psychiatry.
- Dietician (for consideration of ➲ FODMAP diet or alternatives).

Drug treatment

- Analgesics, especially → OPIATES, often not helpful, and side effects such as constipation often compound problem.
- → ANTISPASMODICS can be useful if targeted to patients with cramping abdominal pain. Start with peppermint tea, oil, or capsules, then consider mebeverine 135–150mg PO tds or other similar agents.
- Low-dose antidepressants (e.g. amitriptyline 10–20mg PO nocte can be beneficial, but patients often resistant to idea of taking antidepressants. Important to emphasize (in layman's terms) that at low doses these drugs have visceral analgesic effect rather than psychotropic actions.
- If available, non-pharmacological therapies (such as acupuncture or hypnotism) are often more effective than pharmacological therapies.

Cirrhosis and chronic liver disease

Background

- A diagnosis of chronic liver disease is usually made in patients under investigation for abnormal ➢ LFTs or with unexplained jaundice (see ▶ Approaches to recent-onset jaundice, and ▶ Approach to well patients with abnormal liver tests), or rarely in those who present with ▲ **hepatic encephalopathy** ▲.
- The most common causes in the UK are ➲ alcoholic liver disease, ➲ hepatitis C, and ➲ non-alcoholic fatty liver disease (NAFLD) (see Table 1.10).
- Cirrhosis is a histological diagnosis, characterized by diffuse hepatic fibrosis and nodule formation. Chronic non-cirrhotic liver disease and well-compensated cirrhosis can rarely be differentiated on clinical findings and biochemistry alone (LFTs may be normal, even in established cirrhosis).
- ➲ Liver biopsy should be considered in all cases of chronic liver disease. The exceptions may include patients with clear aetiology of liver disease who have clinically decompensated cirrhosis (e.g. small irregular liver on imaging, with markedly impaired liver function (↑ bilirubin, ↓ albumin, ⇄ prothrombin time) and evidence of ➲ portal hypertension (e.g. ascites, splenomegaly).
- Clinical distinction is often made between patients with compensated cirrhosis and those with decompensated cirrhosis. While distinction may not be absolute, clinical problems and management of these two patterns differ, and so are discussed separately here.

Table 1.10 Causes of cirrhosis and chronic liver disease

➲ Alcoholic liver disease	➲ Haemochromatosis
➲ Hepatitis B	➲ Autoimmune hepatitis
➲ Hepatitis C	➲ Wilson's disease
➲ Primary biliary cholangitis	➲ α_1-antitrypsin deficiency
➲ Primary sclerosing cholangitis	➲ Budd–Chiari syndrome
➲ Drugs (e.g. methotrexate)	Secondary ➲ biliary cholangitis
➲ Metabolic liver diseases	Cryptogenic (≈15%)
➲ Non-alcoholic fatty liver disease	

Compensated cirrhosis

The patient will have preserved liver synthetic function, without ascites or ▲ **hepatic encephalopathy** ▲. The focus of management is to prevent progression (decompensation) and avoid complications.

Management

Treat the cause A nihilistic approach to cirrhosis is not justified. Although the natural course is for progressive fibrosis and liver dysfunction, treatment of the underlying cause has been demonstrated to slow down, and even reverse, clinical progression in patients with established cirrhosis (e.g. ➲ haemochromatosis, ➲ hepatitis B and C). It is vital to address ➲ alcohol use disorder. Promising data are emerging on antifibrotic therapies reversing some effects of cirrhosis, but no agent has been approved yet.

- It is increasingly recognized that ➲ osteoporosis is strongly associated with cirrhosis, especially if cholestatic aetiology (e.g. ➲ primary biliary cholangitis) or on immunosuppression. ⊳ Bone densitometry, p. 167) indicated. Calcium and vitamin D supplements slow progression, and bisphosphonates may be needed (though may cause side effects, including ➲ oesophagitis).
- Complications of ➲ portal hypertension may manifest as acute variceal bleeding (see ▲ **acute upper GI bleeding** ▲), ascites, or ▲ **hepatic encephalopathy** ▲ (i.e. 'decompensated'). After diagnosing cirrhosis, upper GI endoscopy should be considered, as finding gastro-oesophageal varices may merit primary prophylaxis (see ➲ portal hypertension).
- Risk of ➲ hepatocellular carcinoma (HCC) ↑ significantly once cirrhosis develops (e.g. annual incidence of HCC 1–4% in patients with cirrhosis due to ➲ hepatitis C). Evidence supports role for 6-monthly serum ⊳ αFP and US.
- Additional liver insult may lead to decompensation in patients with cirrhosis. Those who may be at any risk of ➲ hepatitis A or B (e.g. frequent travellers to risk areas, drug users, multiple sexual partners) should be tested for immunity, and vaccinated as appropriate.
- Complications of cirrhosis are more common in malnourished patients. Give thiamine 100mg PO bd, encourage high calorie and protein intake, and refer for nutritional advice as necessary (see ► Approach to nutritional support). Note that patients with ➲ alcoholic liver disease may get a high proportion of daily calorie intake from alcohol. A night-time protein snack is therefore recommended.
- Prescribing medication in patients with cirrhosis may be complex, due to the risk of precipitating bleeding (e.g. NSAIDs), worsening liver function, ▲ **hepatic encephalopathy** ▲ (e.g. → OPIATES), or renal impairment (e.g. NSAIDs, aminoglycosides). See also ➲ drug-induced liver injury.
- Pregnancy may occur in cirrhotic patients, although 50% of premenopausal ♀ with cirrhosis have secondary amenorrhea. Close liaison between patient, obstetrician, and hepatologist is essential. See ► Approach to liver problems in pregnancy.

Decompensated cirrhosis

- May be indicated by development of jaundice, ▲ **hepatic encephalopathy** ▲, or ascites. Jaundice and encephalopathy are much more commonly due to acutely deteriorating chronic liver disease than to ▲ **acute liver failure** ▲.
- Decompensation strongly predicts death, with 1 and 5y survival in patients with ➲ Child–Pugh score C of 42% and 21%, compared with 84% and 44% for Child–Pugh score A disease.

Assessment

- Careful history to identify causes of decompensation is vital (see Table 1.11 and Box 1.12). Ask about recent binge drinking (see ➲ alcohol use disorder), any new drugs, infections (common cause, but symptoms and signs of sepsis may be masked in cirrhosis), weight loss, or abdominal pain (e.g. ➲ hepatocellular carcinoma). Has there been any recent change in bowels (melaena, constipation) or haematemesis?
- As well as looking for signs of chronic liver disease (e.g. spider naevi, gynaecomastia—see ➢ GI examination, p. 130), are there signs of decompensation (jaundice, liver flap, ascites)? Assess grade of ▲ **hepatic encephalopathy** ▲. Full general examination to elicit source of possible sepsis (including urine dipstick), and rectal examination to exclude melaena or constipation necessary.

Investigations

- In all cases, blood should be sent for FBC, U&Es, LFTs, glucose, clotting profile, and blood cultures. See also ► Approach to recent-onset jaundice.
- Further investigations will depend on initial results and manifestation of decompensation, but must include a search for precipitant:
    - ➢ αFP.
    - Abdominal US with Doppler of hepatic and portal veins.
    - Culture of urine and sputum.
    - Diagnostic ascitic tap for cell count and culture (see ➢ paracentesis).
    - CXR.

Management

- Directed towards particular manifestation of hepatic decompensation (e.g. ascites) and treatment of precipitants. See other sections:
    - ► Approach to recent-onset jaundice.
    - ► Approach to agitation and confusion in the GI patient.
    - ► Approach to ascites.
    - ▲ **Acute upper GI bleeding** ▲.
    - ▲ **Hepatic encephalopathy** ▲.
    - ➲ Hepatocellular carcinoma.
    - ➲ Hepatorenal syndrome.
    - ➢ Paracentesis.
    - ➲ Portal hypertension.

- In patients with acutely decompensated cirrhosis, discussion with specialist liver service may be appropriate. ➲ Liver support devices, including molecular absorbance recirculation systems (MARS), are not currently licensed for this indication.
- In patients with decompensation due to ➲ hepatitis B, antiviral therapy may improve liver function and clinical disease.
- In view of poor long-term prognosis (e.g. 50% 2y mortality following episode of ascites with ➲ spontaneous bacterial peritonitis), ➲ liver transplantation assessment should be considered once an episode of decompensation has occurred.

Table 1.11 Aetiology of hepatic decompensation

Progressive loss of hepatic function	Dehydration
Additional liver insult (e.g. alcohol, ➲ hepatitis A)	Constipation
▲ **Acute upper GI bleeding** ▲	Renal failure
➲ Hepatocellular carcinoma	Drugs (e.g. opiates)
Infection (e.g. ➲ spontaneous bacterial peritonitis)	Non-compliance with treatment
Increased portosystemic shunt (e.g. ➲ transjugular intrahepatic portosystemic shunt (TIPSS))	Vascular impairment (e.g. acute ➲ portal vein thrombosis)

Box 1.12 Five-point checklist for assessing patient with chronic liver disease

1. Does the patient have cirrhotic or non-cirrhotic chronic liver disease?
2. What's the aetiology?
3. In a patient with cirrhosis, is it well-compensated or decompensated?
4. What interventions may prevent progression to cirrhosis, or to decompensation in a patient with established cirrhosis?
5. What investigations/interventions are needed to avoid/treat complications of cirrhosis?

Constipation

Definition

Defining constipation is hard. In practice, defined by frequency of defaecation twice weekly or less. In reality, many patients complaining of constipation have excessive straining at defaecation (with or without hard stools), a sensation of incomplete evacuation, or excessive time spent on the toilet, even though frequency may be in normal range.

Clinical subtypes and related causes (see Tables 1.12 and 1.13)

Patients may have:

- **Normal transit**, but report hard stools or difficulty in evacuation.
- **Slow colonic transit**, and report ↓ frequency or even absence of urge to defaecate.
- **Incoordination of the rectum, anus, and pelvic floor** with symptoms of straining, incomplete evacuation, and need for anal or vaginal digitation to empty rectum.

Evaluation

History

- **Onset** Constipation from birth suggests congenital cause such as ➲ Hirschsprung's disease.
- **Duration of symptoms** May be of recent onset or chronic. Recent change, particularly in adults, needs work-up for organic causes. Complaints of years' duration are more likely to be functional.
- **Details of bowel habit** Ask about frequency of defaecation, stool form (words like small or hard are subjective; description of 'stringy' or 'pellet-like' stool more helpful), straining, discomfort, sense of incomplete evacuation or 'blockage'. Note any pain or bleeding.
- Associated **abdominal pain or bloating** suggest ➲ irritable bowel syndrome. Associated genitourinary symptoms may suggest underlying central or peripheral neurological disorder.
- **Evacuatory difficulty** Patients will often only admit this if asked directly about need to digitate vaginally or rectally, or need to apply perianal pressure. Vaginal digitation suggests rectocoele, which may need surgical correction.
- Bloating is ubiquitous and does not discriminate functional from organic causes.

- Ask about **laxative use and duration**, and about similar complaints in other family members.
- Ask about mood. Depression, emotional stress, and use of mood-altering drugs, including antidepressants, can affect bowel function.
- Consider the possibility of **sexual abuse**. Somatic reactions to abuse include abdominal pain, constipation, and appetite disturbance.

Table 1.12 Clinical subtypes of constipation

Secondary to an organic colonic cause or outlet obstruction	Recent onset or presence of alarm symptoms indicates need to exclude tumours or stenotic lesions of colon by endoscopy or radiology
Outlet obstruction	Any painful anal condition (e.g. ➔ anal fissure, herpes) or ➔ anal cancer can cause difficulty in defaecation
➔ Irritable bowel syndrome	Consider when coexists with bloating and pain in young person
Constipation with gut dilatation	Causes include idiopathic ➔ megacolon or megarectum, ➔ Hirschsprung's disease, or chronic ➔ pseudo-obstruction
Severe constipation with normal diameter colon	Chronic, often associated with slow colon transit, and most commonly occurs in young ♀ of reproductive age
Drug-induced constipation	See Table 1.13
Constipation secondary to coexisting systemic illness	See Table 1.14
Psychological	➔ Anorexia nervosa, affective disorder, dementia, childhood physical or sexual abuse, loss of parent through death or separation, disturbed toileting behaviour
Constipation due to immobility/age/diet	Elderly or bedridden patients both in and out of hospital may be unable to respond to toileting signals. Can lead to impaction, incontinence, and acute confusional states. Drugs can exacerbate symptoms in this group

Table 1.13 Drugs causing constipation

Drug type	Examples
Analgesics	→ OPIATES
Anticholinergics	Antispasmodics, antidepressants (tricyclics), antipsychotics, antiparkinsonian drugs
Cation-containing agents	Iron, aluminium, calcium, barium, bismuth
Others	Ganglion blockers, vinca alkaloids, anticonvulsants, calcium channel blockers

Examination

- Abdomen for bowel distension, retained stool, and surgical scars.
- Anorectal and perineal examination important.
    - Look for perineal disease or deformity, wasting of gluteal muscles, and rectal prolapse.
    - Digital examination may reveal pain of an anal fissure, anal stenosis, rectal mass, or faecal impaction.
    - Test perineal sensation.
    - Assess anal tone (even though correlation of this with formal anorectal electrophysiological assessment is poor) and ask patient to strain as if passing motion, which can help diagnose prolapse, rectocoele, or abnormal perineal descent.
    - Anismus (paradoxical ↑ in anal tone when straining at stool instead of normal relaxation response) may be seen in victims of rape or sexual abuse.
- Think of non-GI diseases that may cause or exacerbate constipation.
- Do a neurological exam to look for central or peripheral causes. Consider testing autonomic function.

Diagnostic approach and investigations

Most chronically constipated patients do not need extensive investigation.

Structural investigations

Important to exclude organic disease when accompanied by alarm symptoms (recent onset, weight loss, PR blood, family history of ➲ colonic cancer). However, overused in patients with chronic symptoms.

- **Colonoscopy** has relatively little use except to exclude ➲ colonic cancer.
- **Flexible sigmoidoscopy** can help diagnose stenosing left-sided colonic lesions, or laxative abuse via ➲ melanosis coli.
- **Radiology** is sometimes useful. Plain AXR may indicate stool retention and colonic dilatation in megarectum or ➲ megacolon and can help assess efficacy of laxative treatment if clinical uncertainty. Barium studies may show colonic dilatation in ➲ Hirschsprung's disease, but not as useful as physiological studies.
- **Rectal biopsies** can help diagnose ➲ Hirschsprung's disease, but full thickness biopsy is needed.

Functional evaluation (see Fig. 1.4)

For a patient with infrequent defaecation, a prospective 2-week bowel diary and measurement of colon transit time is useful and can distinguish normal from slow-transit constipation. Delayed colon transit can be due to colonic inertia or outlet obstruction. Colonic inertia produces chronic constipation and often responds poorly to medical treatment. If there is excessive straining, transit studies are of little use, but studies of anorectal function may be very useful.

Table 1.14 Systemic diseases causing constipation

Type	Example	Comment
Metabolic/ endocrine	Diabetes	Usually mild but common
	Hypothyroidism Hypercalcaemia Hypokalaemia	
	➔ Porphyria Phaeochromocytoma Glucagonoma	
Central neurological disorders	Multiple sclerosis Parkinson's disease Stroke Cord compression	
Peripheral neurological disorders	➔ Hirschsprung's disease Neurofibromatosis	
	Peripheral nerve damage	Transection of parasympathetic supply in sacral nerves in rectum or cauda equina (injury to lumbosacral spine, meningomyelocele, low spinal anaesthesia) produces colon dilatation, and ↓ rectal tone and sensation. Constipation may occur with high spinal cord lesions, but colon reflexes tend to be intact and defaecation can be triggered by digitation of anal canal
	Autonomic neuropathy Chronic intestinal pseudo-obstruction	
Infiltrative diseases	➔ Systemic sclerosis ➔ Amyloidosis	
Primary muscle disorders	Myotonic dystrophy ➔ Dermatomyositis	

▷ Anorectal manometry is important where compromise of sphincter function is suspected. High resting pressures with absent/↓ reflex relaxation response are seen in ➲ Hirschsprung's disease or defects in afferent sensory pathways (e.g. following spinal cord injuries). Defects in voluntary squeeze imply abnormal external sphincter innervation. Normal voluntary squeeze but low resting pressure indicates a problem with internal sphincter (e.g. after haemorrhoid surgery, with autonomic neuropathy such as in ➲ diabetes mellitus, or with fibrotic disease such as ➲ systemic sclerosis). If manometry is normal, consider anatomical abnormalities such as accentuated puborectalis angulation or internal ➲ rectal prolapse, or (particularly in children) withholding behaviour.

▷ Defaecography or defaecating proctogram may be useful if suspected structural problem influencing defaecation (e.g. rectocoele, prolapse, or intussusception), or to assess functional problems in evacuation. Can be done upright (barium) or supine (MRI).

Treatment considerations

General principles include consideration of ↑ fluid and dietary fibre, adequate toileting arrangements, and avoiding chronic stimulant laxatives if possible.

Diet and the role of fibre

Increasing dietary fibre ↑ stool weight and frequency in healthy people, and constipation may result from dietary fibre inadequacy in some patients. However, there is no evidence that constipated people in general consume less fibre than non-constipated people, and dietary fibre is not usually effective in management of constipated patients referred to hospital. Furthermore, insoluble (cereal) fibre is often poorly tolerated due to bloating and flatulence. Nevertheless, conventional management is to ↑ dietary soluble (fruit and vegetable) fibre to 20–30g/d.

A top ten list of dietary sources of fibre is shown in Table 1.15. The bulking effect of fibre is only partly due to water-retaining capacity; colonic microbial ecology is also important. Fibre can be a substrate for colonic bacteria and ↑ stool bulk by bacterial proliferation and production of stool gases. This partly explains why fibre can provoke abdominal distension and flatulence.

Fibre supplementation is not indicated in patients with ➲ megacolon or megarectum, patients confined to bed, or with neurological disease.

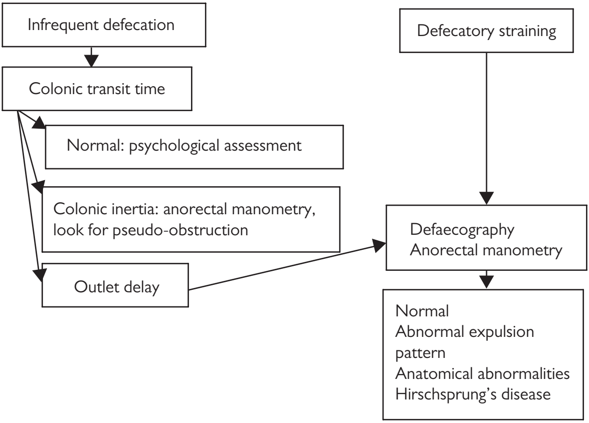

Infrequent defecation
Colonic transit time
Normal: psychological assessment
Colonic inertia: anorectal manometry, look for pseudo-obstruction
Outlet delay
Defecatory straining
Defaecography
Anorectal manometry
Normal
Abnormal expulsion pattern
Anatomical abnormalities
Hirschsprung's disease

Fig. 1.4 Functional evaluation of chronic constipation.

Table 1.15 Food sources of dietary fibre

Food source	Amount of fibre (g) per 100g
Cereals	
All-Bran	26.7
Shredded Wheat	12.3
Cornflakes	11
Whole wheat bread	8.5
Peanuts	9.3
Peanut butter	7.5
Vegetables	
Baked beans	7.3
Peas	6.3
Fruits	
Pear	2.4
Banana	1.7
Apple	1.4

Drugs

Vast amounts of laxatives are consumed, especially by the elderly. Working knowledge of these drug is essential, and the main classes are described in detail in Section 4 (see → LAXATIVES; see also ➲ laxative abuse). For many, laxatives do not provide sustained symptom relief.

- Drugs to ↑ colonic transit are an attractive idea but only partially effective: cholinergic agents or anticholinesterases have been tried in patients with colonic inertia.
- → PROKINETICS include metoclopramide, which is used in upper GI motility disorders, but does not work in colon.
- Prucalopride (a serotonin 5-HT_4 agonist) is licensed in UK for patients who have failed 1st line stool bulking agents or osmotic laxatives. Well tolerated and shown to improve quality of life.
- → LINACLOTIDE is a minimally absorbed peptide agonist of the guanylate cyclase-C receptor, which stimulates intestinal fluid secretion and transit. Licensed for the abdominal pain and bloating associated with chronic constipation.
- Opiate antagonists have been suggested to counteract excessive endogenous opioids. These are under investigation.

Behavioural treatments

Behavioural therapy comprises several components:

- Toilet habit training.
- ➲ Biofeedback therapy (teaching patient to normalize pelvic floor function while watching real-time feedback on sphincter function).
- Psychological support.
- Addressing lifestyle/dietary factors with a view to stopping laxatives is important. Effective for patients with slow-transit constipation or impaired evacuation where traditional treatments have failed (~⅔ patients benefit in terms of symptoms, transit, and quality of life).
- Retrograde irrigation (with anal catheters passed transanally) and connected to a hand-pump driven water reservoir effective licensed option for bowel dysfunction secondary to neurological diseases.

Surgery

- ➔ Hirschsprung's disease.
- ➔ Rectocoele: ≈50% of patients improve after repair. Biofeedback is an option in this group.
- Rectal intussusception and prolapse. Surgery not always curative: intussusception is common in non-constipated people, and its presence in constipated patients is not proof of causation.

Surgical management may be considered for colonic inertia. The most common operation is subtotal colectomy with ileorectal anastomosis. Segmental resection based on removal of that part of the colon with greatest hold-up of markers has not proved effective, and has high rates of anastomotic leakage. Long-term follow-up data indicate success in <50%. The antegrade procedure, where a stoma is made in the caecum and water instilled distally, is another possibility in slow-transit constipation. Sacral neuromodulation (effective in faecal incontinence) has been reported as helpful in refractory constipation as an alternative to colectomy.

Dyspepsia and gastro-oesophageal reflux

Definition

Pain or discomfort in the upper abdomen which, for formal diagnosis, should be present for at least 12wk of the preceding 12 months. Although this definition will capture patients with symptoms of gastro-oesophageal reflux and gastritis, many other conditions also satisfy the same criteria (e.g. cardiac disease, ➲ sphincter of Oddi dysfunction, and pancreatic disease). Subdivisions include 'ulcer-like' (epigastric pain), 'reflux-like' (heartburn and regurgitation), and 'dysmotility-like' (bloating and nausea) discomfort.

Common causes

The most frequent causes are ➲ gastro-oesophageal reflux disease (GORD), ➲ peptic ulceration, and non-ulcer dyspepsia. Most are recurrent and intermittent. The only curative treatments are ➲ *Helicobacter pylori* eradication and surgery (including treatment for ➲ gallstones).

Epidemiology

- Average prevalence in community is 39% when patients with mainly reflux symptoms are included, and 23% when they are not.
- 5% of population consult a GP because of dyspepsia.
- 1% of population are referred for upper GI endoscopy each year. Diagnostic yield is <3% in patients <45y without alarm symptoms (Box 1.13).

Box 1.13 Alarm symptoms prompting urgent investigation of dyspepsia

- Any sign of chronic gastrointestinal bleeding.
- Progressive unintentional weight loss.
- Dysphagia.
- Persistent vomiting.
- Iron-deficiency anaemia.
- Epigastric mass.

When and how to investigate

- Decide if the patient needs urgent referral for investigation (Box 1.13). If there are no alarm symptoms, treat first and investigate later (if necessary).
- Review medications for possible causes of dyspepsia: calcium antagonists, nitrates, theophyllines, bisphosphonates (especially alendronic acid), steroids, NSAIDs, potassium salts, SSRIs.
- Consider cardiac, biliary, or pancreatic disease in differential diagnosis.
- Provide simple lifestyle advice (Box 1.14).
- In those patients needing investigation, endoscopy is the preferred method. Double-contrast barium meal is an alternative in patients unwilling to undergo endoscopy.

Box 1.14 Lifestyle advice for dyspepsia: any use?

All reviews include a section on lifestyle advice, but there is almost no evidence that it makes any difference—except **elevating the head of the bed** to decrease nocturnal reflux (not using extra pillows). Other conventional components include:

- Avoiding eating meals within 4h of going to bed.
- Avoiding late-night alcohol and caffeine (relax LOS).
- Avoid chocolate and fatty foods.
- Weight control, which can ↓ symptoms from hiatus hernia.

Starting treatment

Initial therapeutic strategies for dyspepsia include:

- Empirical treatment with acid suppressants (patients will often have self-medicated with antacids or alginates).
- → PROTON PUMP INHIBITORS are more effective than → H_2 RECEPTOR ANTAGONISTS, safe, and recommended 1st line. Consider addition of H_2RA if inadequate response to PPI.
- Titrate PPI to lowest possible dose to maintain symptom remission.

Testing and treating for ➲ *Helicobacter pylori* (HP)

Testing and treating for HP ↑ response rates compared with antacid therapy alone, and ↓ need for endoscopy. At present, test and treat appears more effective than acid suppression (costs of interventions similar, because HP eradication prevents future development of ➲ peptic ulcers as well as ulcer recurrence). 2 weeks off PPIs necessary before testing for HP using breath test or stool antigen test.

Managing GORD

This includes endoscopically determined ➲ oesophagitis and endoscopy-negative reflux disease (where usually a diagnostic course of acid suppression needed to make diagnosis). Oesophageal mucosal biopsy does not help in diagnosing reflux disease but does help in diagnosing infection, ➲ Barrett's oesophagus, and ➲ oesophageal tumours.

In patients who respond poorly or who have chest pain, 24h pH monitoring may be needed (see ▶ Approach to non-cardiac chest pain).

Treatment of GORD

Most patients can be managed with drugs to lower or neutralize gastric acid (see → ANTACIDS, → PROTON PUMP INHIBITORS, → HISTAMINE RECEPTOR ANTAGONISTS).

- Medical therapy effective at healing oesophagitis and improving reflux symptoms, but drugs do not restore normal antireflux barrier at GOJ. Stopping medication (especially if sudden) often leads to rebound acid hypersecretion, which can precipitate relapse.
- Surgery (see ➢ antireflux procedures) is often proposed as alternative and definitive management. Substantial morbidity and frequent need for medical therapy after surgery means it is not an ideal solution.
- Variety of endoscopic procedures aimed at improving barrier function of lower oesophagus (see ➢ antireflux procedures).

Managing peptic ulcer disease

Although the discovery of HP as the causative agent of 90% of duodenal ulcers (DUs) and 75% of gastric ulcers has led to ↓ incidence of hospitalization and surgery rates for uncomplicated peptic ulceration, there has been little change in the number of admissions for bleeding ➲ peptic ulcer. Overall mortality has remained at ≈6–8% for last 30y, partly due to ↑ patient age and prevalence of concurrent illness.

Initial diagnosis and follow-up

Endoscopy

accurately diagnoses gastric and duodenal ulceration and allows biopsy for malignant change. Also allows diagnosis of many upper GI infections, including HP.

- Endoscopic follow-up is not necessary in patients with uncomplicated DUs whose symptoms resolve on treatment.
- All patients with gastric ulcers need follow-up endoscopy at 6–8wk to confirm ulcer healing. If healing has not occurred, further biopsies are required to exclude cancer.
- Failure of gastric ulcers to heal by 6mo held by many to be an indication for gastric surgery.

Drug therapy with full-dose → PPI or → H_2 RECEPTOR ANTAGONISTS will heal peptic ulcers in majority of cases.

Helicobacter and peptic ulceration

- Eradicate *Helicobacter* in HP-positive patients with peptic ulcer disease. Increases DU healing to 74% after 4–8wk therapy, and ↓ recurrence. Recurrent duodenal ulceration after successful eradication is rare, and usually the result of HP re-infection.
- Eradication does not ↑ gastric ulcer healing but ↓ recurrence.
- Retesting after eradication not suggested as routine, although may be valued by individual patients.
  - In patients with persistent or recurrent symptoms, eradication should be confirmed by stool antigen testing (most sensitive) or carbon-13 urea breath test >4wk after end of treatment. Positive test requires further courses of eradication treatment.
  - Use of serology after treatment not helpful as antibody titres may persist long-term.
  - If stool antigen or breath testing not available, repeat endoscopy may be needed.
  - Antibiotic sensitivity by biopsy and culture, and patient compliance, may need to be checked.
- In patients with complicated DU disease, HP eradication should be confirmed. Some gastroenterologists advocate repeat endoscopy to confirm ulcer healing and biopsies to confirm eradication.

Gastric ulceration

>70% gastric ulcers HP-associated. Biopsies must always be taken to exclude malignancy. Some evidence that gastric brushings for cytology ↑ diagnostic yield.

NSAIDs and peptic ulceration

Risk of ➲ peptic ulceration leading to hospitalization associated with NSAID use ≈ 1 admission/100 patient-years of use in unselected patients. Those with previous history of peptic ulcer at higher risk. Fivefold ↑ in clinically significant GI bleeding in patients on NSAIDs for musculoskeletal pain, and twofold risk for patients taking low-dose aspirin for secondary prevention of cardiovascular disease. See also ➲ non-steroidal anti-inflammatory drugs (NSAIDs) and the GI tract.

- For patients taking NSAIDs with diagnosed peptic ulcer, stop NSAIDs where possible. Treat with full-dose PPI and eradicate HP if present (does not ↑ ulcer healing beyond acid suppression therapy alone, but does ↓ recurrence).
- In patients using NSAIDs who have never had a peptic ulcer, eradicating HP ↓ 1st incidence of peptic ulceration.
- In patients with previous ulcers and in those at high risk, offer gastric protection with PPI/H_2 receptor antagonist. COX-2 selective NSAIDs may be less ulcerogenic, but most clinicians would still combine with gastroprotective agent.
- High-dose PPI or H_2RAs ↓ incidence of endoscopically detected lesions in patients taking NSAIDs.

Non-HP, non-NSAID-associated peptic ulcers

Consider the following causes:

- Failure to detect HP due to PPI or recent antibiotic ingestion.
- Surreptitious or inadvertent aspirin or NSAID use.
- Ulcers related to other drugs: potassium chloride, bisphosphonates, immunosuppressants, and SSRIs all implicated in GI bleeding.
- Acid hypersecreting states, such as ➲ Zollinger–Ellison syndrome (especially if associated with diarrhoea, multiple ulcers, weight loss, hypercalcaemia).
- Crohn's disease.
- TB.
- Malignancy.
- CMV (in immunocompromised).

Managing non-ulcer dyspepsia (NUD)

This includes patients in whom endoscopy has excluded ➲ peptic ulceration (including erosive duodenitis and gastric erosions, considered part of spectrum of peptic ulcer disease), malignancy, or oesophagitis. Patients with dominant heartburn or reflux and no oesophagitis on endoscopy are classified as ‘endoscopy-negative reflux disease’.

There is uncertainty about the cause or best long-term management of these patients (see Box 1.15). Current recommendations include:

Eradicate *H. pylori* if present

In a pooled study of 12 RCTs (2,900 patients) comparing HP eradication with placebo for ↓ dyspeptic symptoms in NUD, response in control group averaged 36% and eradication ↑ this by 7%, with number needed to treat (NNT) =14. If symptoms continue or recur, PPI or H_2RA may be taken ‘on demand’, at lowest dose needed to control symptoms.

Prokinetic drugs

Advocated particularly for dysmotility-predominant patients. Although meta-analysis of 14 trials involving >1,000 patients showed beneficial effect compared with placebo at ↓ dyspepsia in short-term (2–8wk) courses, caution expressed over validity of this result because of heterogeneity of patient inclusion (many trials have not excluded patients with reflux), and inclusion in many studies of the drug cisapride, which has been withdrawn from UK market. Further studies of effectiveness of → DOPAMINE RECEPTOR ANTAGONISTS (e.g. → METOCLOPRAMIDE and → DOMPERIDONE) needed.

Guideline

NICE guideline on gastro-oesophageal reflux disease and dyspepsia (2014).
🖱 https://www.nice.org.uk/guidance/cg184.

Box 1.15 Guidelines for management

NICE guidelines focus on primary care, and are mainly concerned with managing symptoms. Even in patients referred for endoscopy, where prevalence of significant disease is presumed to be greater than in unselected patients in primary care, correlation between symptoms and endoscopic diagnosis is poor. Management in those referred to hospital is based around diagnosis. Two key points are emphasized:

- Urgent specialist referral or endoscopy indicated in patients with dyspepsia of any age when presenting with 'alarm symptoms'.
- Patients >55y with dyspepsia and no alarm symptoms **do not** require routine referral for endoscopy (represents change from previous guidance). However, endoscopy may be considered if symptoms persist despite HP eradication and course of PPI therapy, where there is risk of ➲ gastric cancer, or if anxiety about cancer is heightened (e.g. previous gastric ulcer/gastric surgery, pernicious anaemia).

Why no threshold age for endoscopy in the NICE guidelines?

Previous recommendations for endoscopy recognized that cancer is very rarely found in patients aged <55y without alarm symptoms. However, recent data have extended this as they suggest that an age threshold alone in the absence of alarm symptoms is of little use in predicting cancer.

Eating disorders

Definitions and epidemiology

Defined by abnormal eating habits that negatively impact upon physical ± mental health. The most common are ➲ anorexia nervosa (characterized by extreme low body weight, obsessive fear of weight gain, and unrealistic perception of body weight) and ➲ bulimia nervosa (recurrent binge eating followed by compensatory behaviours such as purging by vomiting, ➲ laxative abuse or use of diuretics, or excessive exercise).

Eating disorders are 10× more common in ♀ than ♂. Women have a 4% lifetime risk of ➲ anorexia nervosa, which carries the highest mortality rate of any psychiatric disorder (with both physical state and suicidal behaviours contributing to risk). Lifetime risk of bulimia 2%. Typically manifest from late childhood or adolescence.

Which patients need admission to a medical bed?

Care settings for patients with eating disorders

Most patients with an eating disorder can be managed in the community. However, if there is refusal to engage in treatment and ➲ body mass index falls to dangerous levels, a setting is required that can provide 24h support and monitoring. This may be a:

- General medical ward.
- General psychiatric ward.
- Specialist eating disorder unit (SEDU).

Key factors influencing the choice of care setting are:

- Acute physiological compromise. Particularly those requiring IV access or cardiac monitoring. Best managed in medical setting.
- Behavioural difficulties. Including sabotage attempts and excessive exercise. Best managed in psychiatric setting.

Frequently, both occur together, in which case correction of life-threatening physiological abnormalities takes precedence over longer-term need to tackle behavioural difficulties; otherwise, default location of care should be a SEDU if available. There may sometimes be confusion among medical staff about the level of treatment possible in psychiatric settings. Designation as a psychiatric intensive care unit or eating disorder high dependency unit is based upon the level of specialist psychiatric input available, not medical resource (see Box 1.16). NG feeding can usually be managed in psychiatric settings, but it would not be unreasonable if that unit asked for the tube to be placed and verified in the medical setting, and for initial few days of feeding to be provided there until ➲ refeeding syndrome can be excluded or managed.

Box 1.16 Level of medical care achievable in SEDUs

Services most units can provide:

- NG tube insertion and feeding.
- Daily biochemical tests.
- Frequent nursing observations.
- Prevention of symptomatic behaviours (water loading, absconding, excessive exercising).
- Daily ECGs.
- Sedation of patients resisting treatment.
- Use and management of mental health legislation.
- Treatment of pressure sores.
- Basic life support.

Services most SEDUs cannot provide:

- Intravenous therapy.
- Cardiac monitoring.
- Artificial ventilation and central line management.
- Parenteral nutrition.
- Cardiac arrest teams.
- Treatment of serious medical complications.

Assessing medical risk

Many patients can seem deceptively well. Can be potent drive to exercise, which can sometimes override lack of nutritional reserve; these individuals may appear highly energetic up to point of collapse. There may be attempts to falsify weights. Features in the history that indicate medical risk are:

- Documented excessive exercise with low weight.
- Inadequate fluid intake in combination with poor eating.
- Rapid weight loss.
- Disruption to ritualized eating habits (travel, holidays, exams).
- Haematemesis.

Clinical assessment

No single measure or assessment tool is an adequate marker of risk in isolation, and therefore the following should be ascertained:

- ➲ **Body mass index (BMI)** Proxy measure of medical risk in ➲ anorexia nervosa. BMI 15–17.5kg/m^2 low risk; 13–15kg/m^2 moderate risk, and <13kg/m^2 high risk. Metabolic changes most problematic if weight changes are rapid, or weight control measures such as vomiting or ➲ laxative abuse are employed. See also 💣Pitfalls box.

- **Muscle strength** Ask the patient to squat on haunches then stand without using arms, and to lie supine on firm flat surface then sit up without using hands.
- **Vital signs:**
  - Heart rate: bradycardia <40/min is concerning.
  - Blood pressure: including postural drop.
  - Core temperature: below 35°C is worrying.
- **ECG** Perform in all patients with BMI <15kg/m^2, HR<40, or drugs that may prolong QT interval (QTc>450ms).
- **Blood tests:**
  - **Sodium** If hyponatraemic, suspect water loading (↓ urine osmolality), diuretic abuse (look for hypokalaemia and hypomagnesaemia), or occult chest infection with secondary SIADH (↑ urine osmolality).
  - **Potassium** If low, be alert for vomiting or laxative abuse.
  - **Renal function** Kidney injury vastly ↑ risks of electrolyte disturbance during refeeding/rehydration (but can be difficult to interpret urea and creatinine if protein intake negligible and muscle mass low).
  - **Other electrolytes** Calcium, magnesium, and phosphate (daily for 1wk, then reduce to twice weekly if normal).
  - **LFTs** ↑ serum aminotransferases occur regularly with severe malnutrition as a result of hepatocellular autophagy. Monitor, but do not usually require detailed investigation and should not divert physician attention away from need to provide nutrition. Hypoalbuminaemia may indicate malnutrition, but can also result from acute phase reaction if there is intercurrent infection.
  - **CRP** Patients with severe malnutrition are functionally immunodeficient and highly susceptible to infections, which may not manifest with typical signs. Search for occult sources of sepsis in patients with ↑ CRP.
  - **Glucose**. Perform point-of-care testing before main meals.

Pitfall. Limitations of BMI in risk assessment in anorexia nervosa

- Potential for deceit.
- Less reliable if there is:
  - Rapid change in weight.
  - Extremes of height.
  - Bulimic features present.
  - Fluid restriction behaviours.
- Underestimates risk in ♂ patients.
- Underestimates risk if medical comorbidity.
- Risk ranges in children vary according to age and development.
- May not detect risks of electrolyte imbalance.

Route of feeding

- Preferred route is oral, although some fail to gain weight.
- Occasionally patients opt for NG feed as feel “less responsible” for weight gain, making it more acceptable.
- Others may resist weight gain by any means, and in such cases compulsory treatment may be necessary (see p. 62).

Transfers

- Aim to transfer to specialist unit as soon as medically stable.
- This period can be high risk, as patients may try to sabotage transfer to units more capable of managing their weight loss behaviours, sometimes to the point of inducing severe physical illness to force retention in a medical bed.
- Ensure all relevant information travels with patient.
- 💣 Occasionally, medical units attempt discharge home once acute medical issue (e.g. hypokalaemia) has been corrected. This is dangerous practice, often motivated by drive to clear beds rather than the clinical needs of the patient. Patients admitted with complications of an eating disorder should not be discharged prior to review by an eating disorders psychiatrist.

Common scenarios

Cardiac dysrhythmias

Common for patients who severely restrict food intake and exercise excessively to present with bradycardia. HR <40/min concerning. May improve with bed rest and nutritional restoration, although if persistent or symptomatic, medical monitoring required.

People with low BMI also vulnerable to prolonged QTc, sometimes further exacerbated by psychiatric medications. SEDUs will not usually have access to cardiac monitoring, nor be able to provide any treatment that requires IV access (e.g. atropine, electrolyte replacement).

Electrolyte disturbances

See also ► Approach to electrolyte disturbance. SEDUs usually able to monitor bloods and ECG daily, as well as oral replacement therapy. Cannot usually offer IV replacement, cardiac monitoring, or formal cardiac arrest team.

Hypokalaemia

- Most often due to purging (vomiting, ➔ laxative abuse, diuretic abuse), but can be secondary to general effects of starvation.
- Potassium <3mmol/L should prompt assessment, particularly in patients who may already be prone to arrhythmias. Acute changes more dangerous that chronically low levels.
- Regular feeding with purging control usually sufficient. If replacement needed, aim to do this slowly, avoiding rapid swings. Oral replacement preferable, where possible.
- → PROTON PUMP INHIBITORS can be useful for preserving potassium by reducing metabolic alkalosis.

- If hypokalaemia refractory, consider sabotage, but also check for ↓ magnesium/calcium, which if present ↑ kaliuresis.

Hyponatraemia

- Can occur due to poor nutrition and salt intake, water loading, or diuretic abuse.
- Plasma sodium <125mmol/L concerning, and acute medical bed may be required to fully assess.
- Management targeted to underlying cause.
- Convulsions cannot be safely managed on SEDU.

Refeeding and underfeeding syndromes

- SEDUs expert in devising food regimes to prevent ➔ refeeding syndrome occurring. However, should it arise, may not be equipped to manage, as requires IV phosphate replacement along with environment where bloods can be processed and acted upon swiftly.
- Involve dieticians early: refeeding syndrome preventable but occurs early and can be difficult to treat once established.
- If admitting patient to medical unit out-of-hours and no dietician immediately available, contact local SEDU as specialist nurses can often advise on appropriate refeeding regimes. NICE guidelines 🖱 https://www.nice.org.uk/guidance/cg32 suggest start 5kcal/kg/d for patients with BMI <14kg/m^2, then building up steadily with close monitoring; however, there are very few published guidelines for anorexia nervosa.
- If really stuck and no help available, unlikely to go wrong offering glasses of (if possible warm) milk. This has high phosphate content and relatively little carbohydrate, so will help rather than exacerbate refeeding syndrome, as well as providing essential calories.
- Often ≈4d oral phosphate supplementation needed. In anorexia nervosa, rare to have isolated deficiency of any one mineral or vitamin, hence multivitamin and mineral replacement recommended (e.g. Forceval® 2 capsules/d).
- Anxiety about causing refeeding syndrome can mean patients experience "underfeeding syndrome", when nutritional compromise severe but insufficient replacement provided, risking further deterioration.

Oedema

Oedema may result from severe hypoalbuminaemia or upon re-introduction of feeding. Both harmless, and resolve within few weeks if nutritional status corrected. Rarely requires specific treatment.

Dysglycaemia

People who have been severely restricting food intake may become hypoglycaemic. Reactive hypoglycaemia can also occur during refeeding syndrome due to initial ↑ in insulin secretion. This may require round-the-clock blood glucose monitoring.

💣Beware combination of eating disorder and type I diabetes mellitus. Patients may feel so overwhelmed by their anorexia nervosa they manipulate insulin doses, leading to recurrent ketoacidosis. Similarly, occasional suicidality and access to readily accessible means can precipitate insulin overdose. It may be necessary for staff to administer insulin or observe injections.

Infection

Patients with low BMI are often pancytopaenic. This generally improves as nutritional state is restored, but in early stages neutropaenia can ↑ vulnerability to infection. Particularly pertinent if NG feeding, as risk of aspiration. Infection may present in unusual ways, so have a low threshold for septic screen. Consider less obvious sources, such as untreated self-harm. Occasionally, G-CSF can be used to stimulate white cell production. This is only ever a temporary measure.

Sabotaging behaviours

Patients with anorexia nervosa often have an extreme compulsion to pursue thinness. If weight gain is less than expected, suspect sabotaging behaviours. Common examples include:

- Artefactually ↑ apparent weight:
  - Drinking water before weighing (consider turning off water supply in room if problematic).
  - Wearing weights.
  - Gripping weighing machine with toes.
- Obsessive exercise: running up and down hospital stairwells, prolonged standing, constant movement (e.g. wiggling toes).
- Wearing little clothing in order to shiver.
- Disposing of food (may recruit friends or relatives to assist).
- Turning off NG feed/IV drips, or running into sink or pillow.
- Removing NG tubes or cannulae.
- Vomiting.

Discovering such activities frequently provokes exasperation and anger among staff. Nonetheless, patients should be regarded as under an irresistible compulsion they are powerless to alter. They may promise to stop, but frequently break this promise. The advantages of SEDUs in this regard include high staff numbers, observable care areas, greater experience managing these behaviours, and behavioural contracts.

Compulsory treatment

In the midst of an eating disorder, patients may be overwhelmed by their illness, rendering it extremely difficult not to engage in self-destructive behaviours. When nutritional restoration is an urgent health need but a person is unable to accept this, compulsory treatment may be necessary. This may be in the form of individualized specialist support from staff or family while the patient feeds themself orally, or NG feeding may be required. In very rare cases, NG feeding under restraint may become necessary. This should be pre-planned, and discussed with all parties involved. In the event sedation is required, use the minimum possible doses as the risk of adverse effects is considerably higher. If patient is at medical risk but does not consent to treatment, they must be:

- Assessed for capacity.
- Treated under appropriate legal criteria if incapacitous.

Mental Capacity Act, 2005

Determining capacity in anorexia nervosa can be complex, as patients may superficially appear to pass assessments. They are usually able to engage in the decision-making process, and it can be complicated to determine whether the decision not to eat is a symptom of mental illness or simply an unwise choice. Even if the patient does initially consent to treatment and is able to acknowledge acute concerns, may renege on decisions when battling high levels of anxiety around mealtimes. Patients with anorexia nervosa can often be extremely persuasive and articulate, and may convince staff to allow them home when this would be against best interests of their health. Be aware that for adolescents between ages of 16–18y, parental consent cannot be used as authority to treat.

People lacking capacity may be treated in their best interests, using the least restrictive option available, so long as this does not deprive them of their liberty and there is no advanced refusal, or objection by a guardian or Court of Protection. Treatment of people with severe anorexia nervosa who are not consenting to feeding will, in most cases, require use of the Mental Health Act, as this involves deprivation of liberty and compulsory nutrition.

Occasionally, patients will present having previously made an Advance Statement or Decision. Some of those who have previously experienced NG feeding may be frightened of the procedure and, when less unwell, be able to indicate what sort of approach they would prefer. This may relate to features of the intervention (e.g. use of narrow-bore NG tubes if possible) or, rarely, refusals of care. If the validity of an Advance Directive is in question, this needs to be carefully evaluated by the psychiatric and medical team, alongside legal assistance.

Mental Health Act (MHA), 1983

A person may be detained for up to 28d for assessment of a mental disorder under Section 2 of the MHA, and for up to 6mo for treatment under Section 3. Although the MHA cannot usually be used to compel treatment for medical conditions, there is an exception for anorexia nervosa. This recognizes the impact of malnutrition on cognitive process and allows feeding against the patient's will. Every attempt must be made to preserve what dignity and autonomy is possible, and the least restrictive approach should be used.

Guidelines

Management of Really Sick People with Anorexia Nervosa (MARSIPAN), Royal College of Psychiatrists and Royal College of Physicians, 2014. 🖱 http://www.rcpsych.ac.uk/files/pdfversion/CR189.pdf.

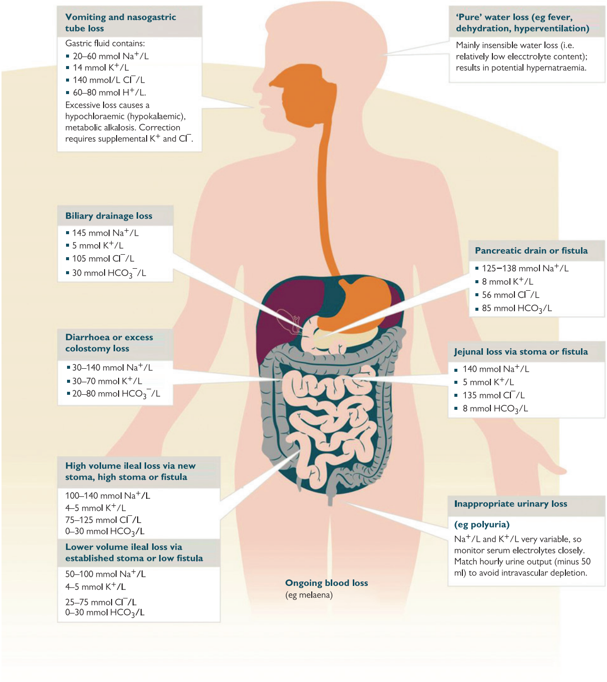
NICE quality statement on eating disorders, 2018. 🖱 https://www.nice.org.uk/guidance/qs175.

NICE guidelines on nutrition support for adults, 2006. 🖱 https://www.nice.org.uk/guidance/cg32.

Electrolyte disturbance

Fluid losses

GI-related electrolyte disturbances are often associated with fluid loss. Guide to sources and concentrations of losses shown in Fig. 1.5.



Vomiting and nasogastric tube loss

Gastric fluid contains:

- 20–60 mmol Na^+/L
- 14 mmol K^+/L
- 140 mmol/L Cl^-/L
- 60–80 mmol H^+/L.

Excessive loss causes a hypochloraemic (hypokalaemic), metabolic alkalosis. Correction requires supplemental K^+ and Cl^-.

Biliary drainage loss

- 145 mmol Na^+/L
- 5 mmol K^+/L
- 105 mmol Cl^-/L
- 30 mmol HCO_3^-/L

Diarrhoea or excess colostomy loss

- 30–140 mmol Na^+/L
- 30–70 mmol K^+/L
- 20–80 mmol HCO_3^-/L

High volume ileal loss via new stoma, high stoma or fistula

100–140 mmol Na^+/L
4–5 mmol K^+/L
75–125 mmol Cl^-/L
0–30 mmol HCO_3/L

Lower volume ileal loss via established stoma or low fistula

50–100 mmol Na^+/L
4–5 mmol K^+/L
25–75 mmol Cl^-/L
0–30 mmol HCO_3/L

'Pure' water loss (eg fever, dehydration, hyperventilation)

Mainly insensible water loss (i.e. relatively low elecctrolyte content); results in potential hypernatraemia.

Pancreatic drain or fistula

- 125–138 mmol Na^+/L
- 8 mmol K^+/L
- 56 mmol Cl^-/L
- 85 mmol HCO_3/L

Jejunal loss via stoma or fistula

- 140 mmol Na^+/L
- 5 mmol K^+/L
- 135 mmol Cl^-/L
- 8 mmol HCO_3/L

Inappropriate urinary loss

(eg polyuria)

Na^+/L and K^+/L very variable, so monitor serum electrolytes closely. Match hourly urine output (minus 50 ml) to avoid intravascular depletion.

Ongoing blood loss
(eg melaena)

Fig. 1.5 Diagram of ongoing losses.

Reproduced from National Clinical Guideline Centre, 'Intravenous fluid therapy in adults in hospital', NICE clinical guideline 174 (December 2013) © National Institute for Health and Care Excellence 2013.

Sodium

Disorders of plasma sodium balance are not necessarily caused by absolute salt excess or deficit, but reflect an imbalance with the amount of free water.

Hyponatraemia

Symptoms and signs

Manifestations depend on magnitude and rate of drop. Symptoms usually subtle above 125mmol/L, but below include altered mental status, anorexia, nausea, confusion, seizures, and coma.

Investigation

A useful algorithm is shown in Fig. 1.6. Important points:

- Exclude pseudohyponatraemia. Measure serum lipids and protein (excess can cause artefactual ↑ in measured plasma volume and apparent dilution, although less of an issue with modern analysers). Reported Na^+ will be low but plasma osmolality normal).
- Check plasma glucose. If >20mmol/L, correct measured Na^+ concentration by adding 4.3mmol/L for every ↑ in glucose of 10mmol/L above normal. Plasma osmolality will be high.
- Review patient's medication (most common cause of hyponatraemia, particularly thiazide diuretics). Discontinue where appropriate. See Table 1.16 for other drug causes.
- Determine volume status. This is the most important guide to diagnosis and management.

Treatment

Do not base treatment on plasma Na^+ concentration alone. Management depends on underlying cause, presence of symptoms, and duration and rapidity of its development.

- GI losses best corrected using ➔ oral rehydration salts or IV 0.9% saline. Monitor and replace other electrolytes that may be lost via same processes (particularly K^+ and Mg^{2+}).
- Aim to correct by no more than 0.5mmol/L/h, and 15mmol/L/24h. More rapid correction may cause pontine myelinolysis.
- Where possible, treat underlying cause. If this cannot be definitively identified, and active treatment indicated, fluid restriction to <1.5L/24h can be instigated. Note this will cause Na^+ to ↑ *irrespective* of the underlying pathology, but may have other detrimental effects on fluid balance.
- If need to treat acutely (i.e. severe symptoms), 100ml boluses of 3% saline IV can be given over 15min-1h in highly monitored settings.
- Occasionally demeclocycline or vasopressin receptor antagonist (vaptan) drugs may be required. Seek expert advice on use and dosing.

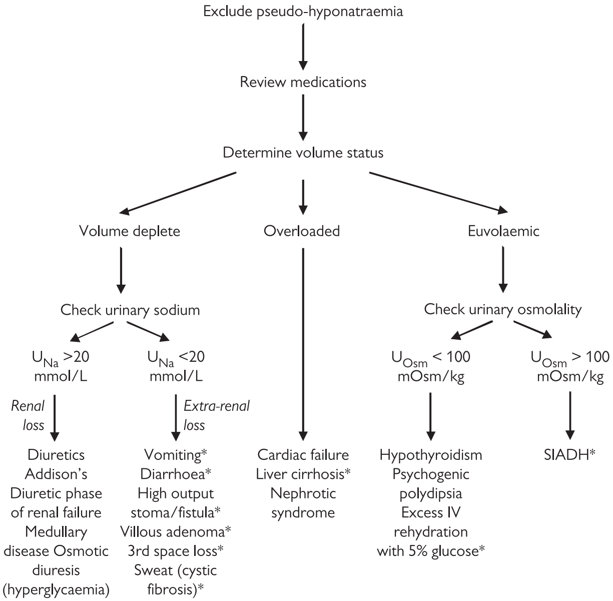

Exclude pseudo-hyponatraemia
Review medications
Determine volume status
Volume deplete
Overloaded
Euvolaemic
Check urinary sodium
Check urinary osmolality
U_{Na} >20 mmol/L
U_{Na} <20 mmol/L
U_{Osm} < 100 mOsm/kg
U_{Osm} > 100 mOsm/kg
Renal loss
Extra-renal loss
Diuretics
Addison's
Diuretic phase of renal failure
Medullary disease Osmotic diuresis (hyperglycaemia)
Vomiting*
Diarrhoea*
High output stoma/fistula*
Villous adenoma*
3rd space loss*
Sweat (cystic fibrosis)*
Cardiac failure
Liver cirrhosis*
Nephrotic syndrome
Hypothyroidism
Psychogenic polydipsia
Excess IV rehydration with 5% glucose*
SIADH*

Fig. 1.6 Investigation of hyponatraemia. *Causes relevant to GI tract shown by asterisks.

Table 1.16 Drug causes of hyponatraemia

Diuretics	Opiates
Carbamazepine	NSAIDs
Antidepressants	Cyclophosphamide
Chlorpropamide	Haloperidol
Ecstasy (MDMA)	→ PROTON PUMP INHIBITORS

Hypernatraemia

In contrast with the more complex aetiology of hyponatraemia, hypernatraemia almost invariably results from dehydration, with excess free water loss compared with sodium. This may very occasionally be due to inappropriate excessive IV volume replacement with saline.

Symptoms and signs are those of thirst, progressing through to confusion, convulsions, and eventually coma. These are usually accompanied by clinical evidence of volume depletion.

Mainstay of treatment is cautious rehydration, which should be attempted orally if possible and hypernatraemia is mild, but otherwise via the IV route. It is usually appropriate to replenish intravascular volume with 0.9% saline, as this will be hypotonic with respect to plasma in the hypernatraemic patient. In general, fluids such as 5% glucose should be avoided as they may generate more substantial fluid shifts, risking pontine myelinolysis.

Potassium

Potassium ions are predominantly intracellular. Alterations in serum concentration reflect changes in intake or excretion, or redistribution between intracellular and extracellular compartments (Tables 1.17 and 1.18).

Hypokalaemia

Symptoms and signs

Muscle weakness, hypotonia, cramps, tetany, cardiac dysrhythmias. ECG changes: small/inverted T waves, U waves, ↑ PR interval, ST depression.

Table 1.17 Causes of hypokalaemia

Redistribution	Excess loss
Alkalosis	Diuretics (thiazides, loop)
β_2 adrenergic agonists	Vomiting/diarrhoea
Hypokalaemic periodic paralysis	Pyloric stenosis
	Villous adenoma of the rectum
	Intestinal fistulae/high-output stoma
	Cushing's/Conn's syndromes
	Purgative abuse
	Liquorice

Treatment

Mild hypokalaemia (2.5–3.5 mmol/L, no symptoms/ECG changes) can be treated with oral supplements (e.g. Sando-K® 2–3 tablets bd).

In severe hypokalaemia (<2.5mmol/L or symptomatic with ECG changes), or when oral route unavailable or inappropriate (high-output stoma), replacement should be IV. Potassium should be given no faster than 20mmol/h (& usual rate more conservative at 10mmol/h) or at concentrations >40mmol/L. Caution is advised in oliguric patients. *Stat boluses should never be given.*

❗ Note that it is extremely difficult to correct hypokalaemia in presence of concurrent hypomagnesaemia.

Hyperkalaemia

Symptoms and signs

Main concern is cardiac dysrhythmia. ECG changes progressive and include tall tented T waves, small P waves, and widening QRS complexes through to development of sinusoidal morphology and degeneration into ventricular fibrillation.

Table 1.18 Causes of hyperkalaemia

Excess intake	Redistribution	Reduced loss
Iatrogenic	Acidosis	Renal failure
Multiple blood transfusions	Burns	Potassium-sparing diuretics (ACE inhibitors, angiotensin receptor blockers, spironolactone, amiloride)
	Rhabdomyolysis	Addison's disease
	Suxamethonium	

Treatment

Serum potassium >6.5mmol/L requires immediate action. Stop all potassium supplements and potassium-sparing diuretics, and initiate investigation for the underlying cause.

- Perform ECG. If changes due to hyperkalaemia, administer 10ml of 10% calcium chloride or calcium gluconate as slow IV bolus (maximum 2ml/min). This is cardioprotective, but does not alter serum K^+. ❗ *May be hazardous for patients on digoxin, although this is still debated.*
- Add 10 units soluble insulin to 100ml of 20% glucose (or 50ml of 50% glucose) and infuse over 15min. Monitor blood glucose levels prior to starting and every 30min for 2h. ❗ *Insulin shifts potassium intracellularly and only temporarily ↓ plasma concentration.*
- Nebulized salbutamol (5mg) is also effective at temporarily redistributing potassium to intracellular compartment.
- To ↑ potassium excretion, administer calcium polystyrene sulfonate 15g every 8h PO, with regular lactulose (10–20ml PO bd). Alternatively, administer as retention enema (30g tds).
- If serum K^+ is resistant to these measures, refer to renal unit/intensive care for haemofiltration/haemodialysis.

Calcium

≈40% of circulating calcium bound to albumin. Measured serum concentration therefore needs to be corrected according to albumin level. If this value needs to be calculated, formula (in mmol/L) is:

$$Ca^{2+}{}_{\text{corrected}} = Ca^{2+}{}_{\text{measured}} + \left[0.025 \times (40 - \text{albumin})\right]$$

Calcium homeostasis is governed by number of hormones, which usually exert simultaneous effects on serum phosphate.

- Parathyroid hormone: $\uparrow Ca^{2+}$, $\downarrow PO_4^{3-}$.
- Vitamin D: $\uparrow Ca^{2+}$, $\uparrow PO_4^{3-}$.
- Calcitonin: $\downarrow Ca^{2+}$, $\downarrow PO_4^{3-}$.
- Thyroxine: $\uparrow Ca^{2+}$ (rarely).
- Hypomagnesaemia prevents PTH release, and ∴ may cause $\downarrow Ca^{2+}$.

Hypocalcaemia

Symptoms and signs

Depression, peripheral and perioral paraesthesia, carpopedal spasm. Trosseau's sign (carpopedal spasm on inflating tourniquet on limb) and Chvostek's sign (tapping over inferior zygoma causing excitation of facial nerve and facial twitching) may be elicited. ECG: ↑ QT.

Causes

Diagnosis guided by serum PO_4^{3-} concentrations (see Table 1.19).

Table 1.19 Causes of hypocalcaemia

↑ PO_4^{3-}	Normal or ↓ PO_4^{3-}
Hypoparathyroidism	Osteomalacia (↓ ALP)
Pseudohypoparathyroidism	Overhydration
Chronic renal failure	Pancreatitis
Rhabdomyolysis	

Treatment

If mild, give oral calcium supplements 5mmol/6h. In chronic renal failure, may be necessary to add alfacalcidol 0.5–1μg/24h.

If hypocalcaemia is severe or accompanying ECG changes, supplement IV with 10ml of 10% calcium chloride or gluconate, diluted in 100ml 0.9% saline over 30min.

Hypercalcaemia

Symptoms and signs

'Bones, stones, abdominal groans, and psychic moans.' Also anorexia, vomiting, constipation, polydipsia, polyuria, weakness, hypertension, and renal failure. ECG: ↓ QT.

Causes

Diagnosis is guided by serum albumin, PO_4^{3-}, PTH, and ALP (Fig. 1.7).

Treatment

Mainstay is to address underlying cause. For calcium levels >3.5mmol/L, rehydrate with 0.9% saline, aiming to achieve 4–6L/24h. If calcium remains elevated despite adequate rehydration, can try:

- Bisphosphonates. Infuse pamidronate no faster than 30mg in 300ml 0.9% saline over 3h via large vein (see Table 1.20). Reduction in Ca^{2+} occurs over 48–96h.
- Furosemide 40mg IV bd (avoid thiazides, which elevate Ca^{2+}).
- Steroids can be effective in sarcoid, as can chemotherapy in hypercalcaemia associated with malignancy.
- Salmon calcitonin rarely required.

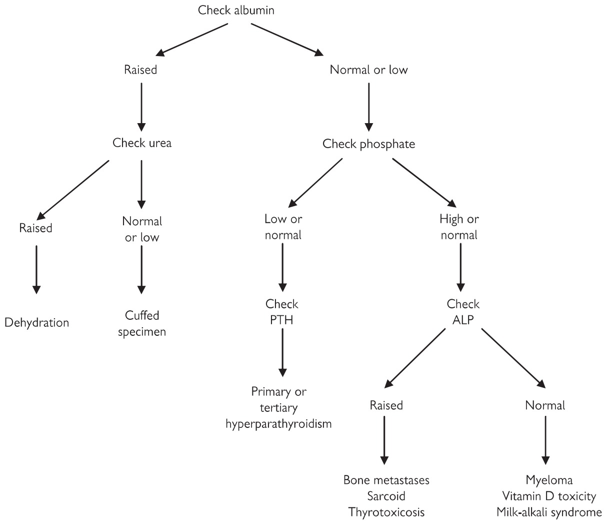

Check albumin
Raised
Normal or low
Check urea
Check phosphate
Raised
Normal or low
Low or normal
High or normal
Dehydration
Cuffed specimen
Check PTH
Check ALP
Primary or tertiary hyperparathyroidism
Raised
Normal
Bone metastases
Sarcoid
Thyrotoxicosis
Myeloma
Vitamin D toxicity
Milk-alkali syndrome

Fig. 1.7 Diagnosis of hypercalcaemia.

Table 1.20 Bisphosphonate dosing in hypercalcaemia

Serum calcium (mmol/L)	Pamidronate dose (mg)
<3	15–30
3–3.5	30–60
3.5–4	60–90
>4	90

Magnesium

Plasma Mg^{2+} concentration tends to follow those of K^+ and Ca^{2+}.

Hypomagnesaemia

See Box 1.17 for causes.

Symptoms and signs

Paraesthesia, fits, tetany, and cardiac dysrhythmias.

Box 1.17 Causes of hypomagnesaemia

Diarrhoea, high-output stoma/fistula
Acidosis
Alcohol misuse
Parenteral nutrition
Concurrent hypocalcaemia/hypokalaemia
Diuretics (particularly thiazide and loop)

Treatment

If serum concentration >0.5mmol/L, give oral magnesium glycerophosphate 2–5 tablets tds. If concentration <0.5mmol/L or enteral route not available, give IV magnesium sulfate 8–20mmol in 100ml 0.9% saline over 30min.

Hypermagnesaemia

Almost always iatrogenic, or due to use of excess antacids or renal failure. Treat if symptomatic.

Symptoms and signs

Altered GCS, neuromuscular depression, hypotension, coma.

Treatment

If renal function normal, give IV furosemide. If in renal failure, refer for haemodialysis/haemofiltration.

Phosphate

Phosphate plays an important role in many metabolic functions, as well as neuromuscular membrane stability.

Hypophosphataemia

See Box 1.18 for causes.

Symptoms and signs

Muscle weakness (including extraocular muscles, cardiac, respiratory, and gastrointestinal), altered conscious level, irritability, confusion, coma, immunocompromise.

Box 1.18 Causes of hypophosphataemia

➔ Refeeding syndrome
Alkalosis
Alcohol misuse
Malabsorption (secondary to ↓ vitamin D)
Chronic use of phosphate binders (sucralfate, antacids)
Phosphaturia (primary, or secondary to hyperparathyroidism)

Treatment

If asymptomatic with serum concentration 0.4–0.6mmol/L, give Phosphate-Sandoz® 2 tablets PO bd.

If symptomatic at these concentrations, enteral route not available, or serum concentration <0.4mmol/L, give phosphate Polyfusor® IV. Each Polyfusor® bag contains 50mmol phosphate in 500ml (also contains 9.5mmol potassium and 81mmol sodium). Usual prescription 9mmol over 12h (i.e. run at 7.5ml/h). Levels should be repeated at this time, and further phosphate prescribed if needed. Up to 50mmol can be administered over 24h in intensive care setting with close monitoring.

Hyperphosphataemia

Symptoms and signs

Chronic hyperphosphataemia causes ectopic calcification and osteodystrophy.

Causes

Hypoparathyroidism, chronic renal failure, iatrogenic.

Treatment

- Dietary restriction of high phosphate foods and supplements.
- Phosphate binders (aluminium hydroxide, calcium carbonate).

Faecal incontinence

Common problem (up to 2% of people faecally incontinent once/week). Frequently difficult for patients to discuss with doctors or relatives, and direct questioning often necessary, as is an understanding of continence mechanisms (Box 1.19). Continence depends on sphincter muscles (Fig. 1.8), stool consistency, and cognitive factors.

Box 1.19 Continence mechanisms

- Spongy vascular tissues within anal canal play minor role in continence by assisting anal closure. Minor seepage may be seen after partial excision of this tissue at haemorrhoidectomy.
- Major mechanisms of continence depend on anal sphincters. Internal sphincter is continuation of circular muscle layer and under autonomic control. Contributes 70% of resting anal tone. External sphincter striated, and supplied by sacral nerves S2–4. Tonic neural activation contributes 30% of resting tone, but voluntary squeeze of external sphincter during distension can double this.
- Puborectalis muscle wraps around anorectal junction, forming a sharp angle between rectum and anal canal (Fig. 1.8a). Relaxation of puborectalis allows straightening of rectoanal angle for defaecation (Fig. 1.8b).
- Anal canal very sensitive to touch, pain, and temperature, which allows discrimination of solid, liquid, and gas contents, enabling selective passage of these materials.
- Rectal sensation and compliance important for maintaining continence. Neuropathies can impair sensation and compliance may be reduced by radiation, colitis, or ischaemia.

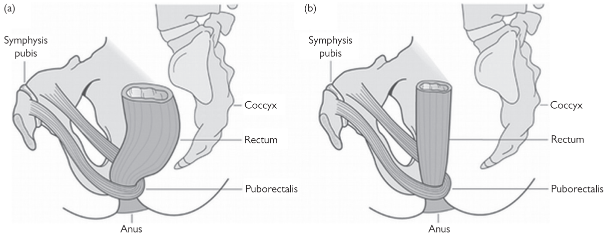


Fig. 1.8 Mechanism of action of puborectalis muscle in maintaining faecal continence.

Clinical evaluation

History

Ask about:

- Passive and urge incontinence.
- Duration and severity.
- Solid, liquid, or gas? A slight stain on underpants or whole stool?
- Coincident urinary incontinence.
- Potential causes:
  - Obstetric history, including maximum birth weight, instrumentation, tears/episiotomies, presentation of baby (e.g. occipito-posterior).
  - Previous anal surgery.
  - Other systemic/neurological symptoms or diagnoses.

Examination

Routine examination, including perianal examination, rectal exam (look for faecal impaction) and sigmoidoscopy (rectal inflammation, mucus-secreting polyp such as villous adenoma) essential. Important to assess anal tone and squeeze pressure, but digital examination correlates poorly with operative and histological findings. Causes of incontinence lists in Table 1.21.

Investigation

Include ➢ anorectal physiology and ➢ endoanal US.

Treatment

Conservative

Include → ANTIDIARRHOEAL AGENTS (e.g. loperamide, titrated to achieve beneficial effect), mechanical barriers, or behavioural treatments including ➲ biofeedback, which is effective even in patients with structural sphincter damage.

Surgical

- As a minimally invasive surgical approach, sacral nerve stimulators may help, and have benefit that temporary wire can initially be tried to assess for efficacy.
- Surgery should be reserved for patients with major faecal incontinence in whom conservative methods have failed. External sphincter can sometimes be repaired after obstetric disruption with an overlap repair. Internal sphincter not amenable to surgical repair.
- Repair of a prolapse may be possible by rectopexy.
- Other surgical treatments include dynamic graciloplasty, which involves continuous electrical stimulation of gracilis muscle using implantable pulse generator. Unfortunately, there is considerable associated morbidity.
- An artificial anal sphincter can deliver significant clinical improvement, but again limited by complications, including explantation in up to ⅓ patients.
- Colostomy remains an alternative that can return the patient to near-normal lifestyle.

Table 1.21 Causes of faecal incontinence

Internal anal sphincter degeneration	Most common cause in the elderly
Obstetric trauma	⅓ of primiparous women have some damage to anal sphincter after 1st delivery. Forceps delivery, large baby, and occipitoposterior position are risk factors
Surgical damage	Surgically induced sphincter damage can occur after lateral sphincterotomy or major colonic resection
Anal dilatation	Incontinence may complicate manual dilatation of anus (which used to be performed for ➔ anal fissures) or anal fistulae passing through sphincter muscles. Receptive anal intercourse also risk factor
➔ Rectal prolapse	Incontinence in 30–80%. EUS can help in diagnosis
Congenital	Half of all patients with spina bifida soil regularly. ⅓ of children operated on for ➔ Hirschsprung's disease incontinent at age 4. Soiling may complicate surgery for sacral tumours
Spinal injury	Soiling occurs in 30% patients with multiple sclerosis
Radiation injury (see ➔ radiation damage to the GI tract)	Radiation to anorectum combined with proctitis and reduction in compliance can produce incontinence
Systemic disease	Diabetics can have somatic and autonomic neuropathy. In ➔ systemic sclerosis, internal sphincter muscle atrophy, acquired megacolon, and ➔ bacterial overgrowth can all occur

Gastrointestinal problems in elderly patients

GI disease is more common in the elderly. In most cases, age has little effect on management. Several interlinked factors contribute to the high rate of symptoms:

- **Malignancy** All major GI tract cancers ↑ in prevalence with age, with steep rise after 60y (e.g. ➲ gastric, ➲ oesophageal, ➲ pancreatic, ➲ colonic cancer).
- **Comorbidity** Examples are ➲ Parkinson's disease (leads to constipation through autonomic dysfunction and secondary to anticholinergic drugs), motor neurone disease (dysphagia—see ► Approach to mouth and swallowing), and Alzheimer's disease (poor nutrition, ➲ faecal incontinence).
- **Drug effects** Motility disorders, especially constipation, promoted by wide range of drugs: e.g. → ANTICHOLINERGICS, antidepressants, → OPIATES. NSAIDs for joint pain contribute to ➲ peptic ulceration.
- **Immobility** Leads to GI motility problems for a range of reasons, including embarrassment at needing assistance, associated depression, and antiphysiological posture for defaecation (being supine/semi-supine). Supine position may also encourage gastro-oesophageal reflux.
- **Nutrition** Malnutrition prevalent in elderly (weight loss is a predictor of mortality), particularly if hospitalized, socially isolated, or with mental//physical health problems. Patients following stroke, severe hand arthritis, tremors, or dementia may require extra assistance. Dental condition and visual problems may further impact on oral intake. In those with severe dementia and inadequate nutrition, difficult ethical considerations surround use of artificial feeding (see ► Approach to nutritional support).

General approach

It is particularly important in this patient cohort to pay attention to more subtle or non-specific symptoms, and recognize the importance of maintaining function. Broader geriatric assessment should include activities of daily living, cognitive function, and symptoms of depression (may manifest with weight loss, pain, or altered bowel habit). In addition, physiological changes in liver and renal function, as well as body composition, can affect drug pharmacokinetics, ↑ risk of side effects.

Specific conditions

Constipation

- 25% prevalence of constipation/straining in elderly living at home (↑ to 50% in those in hospital/institutional care).
- Most commonly due to slow-transit or dyssynergic defaecation.
- Faecal impaction and incontinence in >10% of those >75y.

- Poor fluid intake, immobility, and drugs all contribute.
- Laxatives used regularly by 20–30% of people >65y.
- In hospital patients, stimulant/osmotic → LAXATIVES are more effective than fibre, which may encourage faecal impaction in immobile patients.
- If faecally impacted, consider suppositories, enemas, or manual disimpaction.

Dyspepsia

Common practice of performing endoscopy in all elderly patients with new-onset dyspepsia recently challenged by NICE guidelines. These advise that endoscopy should not be 'age-dependent', and that endoscopy for dyspepsia should be reserved for those with warning symptoms (see ▶ Approaches to dyspepsia and reflux).

▲ ***Acute abdominal pain*** ▲

In elderly patients, the usual peritonitic response to viscus perforation or other acute abdominal event (e.g. ➔ intestinal ischaemia) may be blunted, leading to typical presentations being masked and hence late diagnosis. ❗ *An "acute abdomen" is a ruptured aortic aneurysm or ischaemic bowel (especially if ↑lactate) until proven otherwise.*

➔ *Gallstones*

For patients with bile duct stones, ERCP with sphincterotomy and stone extraction should be considered in all, as morbidity occurs in 40% of elderly patients in whom long-term biliary stenting alone is performed. ➢ Cholecystectomy generally safe in the elderly.

Endoscopy in the elderly patient

- Never assume that a patient is not a candidate for treatment based on age alone, but be alert for evidence of cognitive impairment that may impact on capacity and validity of consent.
- Assessment of functional status and social circumstances is important to identify any factors that may limit patient attendance at hospital, and care in recovery phase after procedure.
- Most aspects of preparation (e.g. period of NBM) similar, but be more cautious with bowel prep (be wary of profound fluid and electrolyte shifts, particularly in patients with underlying cardiac or renal dysfunction). Unfortunately, this does mean inadequacy of bowel prep can be higher in elderly patient (up to 20% suboptimal).
- Monitoring during procedure is the same as for younger patients. However, there is ↑ risk of aspiration and hypoxia (due to ventilation/perfusion mismatch), and ↑ sensitivity to sedatives (use fewer agents, at slower rates, with lower initial and cumulative doses).
- ➢ ERCP and ➢ colonoscopy safe in appropriately selected patients. Frailty greater determinant of adverse outcome than age.
- ➢ Percutaneous endoscopic gastrostomy (PEG) placement is controversial in dementia, as 30d mortality ≈20% (mostly related to comorbidities rather than procedure). See 💣 Controversies box.

💣 Controversy. Tube feeding in advanced dementia

- Tube feeding is a medical therapy, not a basic provision of comfort. Neither patients nor their relatives can demand tube feeding be instituted, although it may be refused by patients with capacity, those with advance directives or with a medical power of attorney.
- Careful hand feeding should be offered. This is at least as good as tube feeding for outcomes of death, aspiration pneumonia, functional status, and patient comfort; and superior for agitation, use of sedation, and limiting development/progression of pressure sores.
- Voluntary cessation of nutrition (and hydration) is a medically, ethically, and legally acceptable step that patients (or those responsible for their care) may choose. Nonetheless, be sensitive that nutrition and hydration can have symbolic value for family. Reasonable to respect their point of view as long as it does not conflict with a patient's previously expressed wishes, or appears to be causing distress.

Gastrointestinal problems in pregnancy

Gastrointestinal symptoms are common in pregnancy and can be more challenging to investigate and treat. They can arise from:

- changes in gut motility and tone
- effects of gravid uterus.

Abnormal liver function in pregnancy is discussed separately (see ▶ Approach to liver problems in pregnancy).

Nausea and vomiting

Nausea occurs in 50–90% of pregnant ♀ (often during Weeks 6–8), and 25–55% experience vomiting. Often termed 'morning sickness', although a significant percentage suffer throughout day. **Risk factors** include young maternal age, smoking, 1st pregnancy, multiparity, and history of motion sickness. It is self-limiting in most cases, with no need for specific investigation, but assessment is necessary to exclude other causes (e.g. UTI).

Management

- Mild symptoms may respond to reassurance and dietary change (small regular meals).
- Antiemetics, including → DOPAMINE ANTAGONISTS (e.g. metoclopramide) and → ANTIHISTAMINES (e.g. cyclizine) used in severe cases. → ONDANSETRON not specifically licensed in pregnancy, and concerns that may ↑ risk of cleft palate.
- Pyridoxine and ginger root may be beneficial.

Hyperemesis gravidarum

Characterized by intractable vomiting. Occurs in 0.1% of pregnancies, with onset usually in Weeks 6–8. Dehydration, hypovolaemia, and metabolic disturbance (ketosis, metabolic alkalosis, ↓ Na^+, ↓ K^+) may result, and can occasionally be life-threatening.

Management

- Admission to hospital. This, and addressing possible psychosocial problems, may improve symptoms.
- Take blood for FBC, clotting, U&E, LFTs, Glu, Ca^{2+}, Mg^{2+}, HCO_3.
- IV rehydration with 0.9% normal saline & K^+ supplements. Avoid rapid correction of ↓ Na^+ (may cause central pontine myelinolysis).
- Give thiamine 150mg PO od, or 100mg IV weekly) to prevent ➲ Wernicke's encephalopathy.
- Antiemetics are usually used, including metoclopramide 10mg PO/IV/IM tds or cyclizine 50mg IV tds.

- If vomiting continues, ➲ parenteral nutrition may sometimes be needed. See ▶ Approach to nutritional support.
- Acid suppression can help.

Despite its symptomatic severity, the outcome of pregnancy complicated by hyperemesis gravidarum is no different from general population.

Heartburn and reflux symptoms

Symptoms of ➲ GORD occur in >50% of pregnant ♀, probably due to combined effects of ↓ gastric emptying, relaxation of lower oesophageal sphincter, and in 3rd trimester ↑ abdominal pressure due to gravid uterus.

- Endoscopy and investigation for disorders of oesophageal motility almost never necessary.
- Antacids may be liberally used (as not systemically absorbed), with advice to eat small regular meals and elevate head of the bed.
- → H_2 RECEPTOR ANTAGONISTS are next line of treatment (ranitidine 150mg PO bd), and were effective in randomized trials.
- While → PROTON PUMP INHIBITORS appear safe, experience of their use is less than that of → H_2 RECEPTOR ANTAGONISTS, so typically reserved for ♀ with severe symptoms. Only omeprazole is licensed in UK for use in pregnancy. See also ▶ Approach to dyspepsia and gastro-oesophageal reflux.

Abdominal pain

- ▲ **Acute abdominal pain** ▲ in pregnancy may represent a particular diagnostic and management challenge, due to several factors:
  - Clinical confusion with pregnancy-associated symptoms due to episodic uterine contractions ('Braxton–Hicks'), true labour, or pressure effects from gravid uterus.
  - Atypical presentation of GI disease in pregnancy.
  - Reluctance to use invasive investigation (e.g. endoscopy) or radiation (e.g. CT).
- Gallbladder sludge can be shown in 30% of pregnancies, and asymptomatic ➲ Gallstones in up to 11%. ➲ Cholecystitis develops in 0.1%, and biliary obstruction and gallstone ➲ Pancreatitis may occur. ➢ Cholecystectomy may occasionally be necessary, and is 2nd most common non-obstetric indication for surgery during pregnancy (behind appendectomy—see ➲ appendix and appendicitis). Surgery is probably safest in the 2nd trimester.

- ⊳ ERCP may be necessary for biliary obstruction. Perform only if absolutely necessary, but appears safe. In view of radiation exposure, screening time should be kept to a minimum; lead protection for the foetus is essential, and ideally procedure should be avoided in the 1st trimester.
- Symptoms of ectopic pregnancy, including rupture, usually develop in Weeks 5–8, with localized pain, peritonitis, and shock secondary to haemorrhage. May be a surgical emergency.
- ➲ Peptic ulceration may present in pregnancy, but appears less common than in the non-pregnant population.

Constipation

Affects >30% of pregnant ♀, because of combination of ↓ motility and water reabsorption. ↑ fibre and fluid usually helps, but osmotic laxatives and bulking agents are often effective. Castor oil should not be used.

Diarrhoea

No ↑ incidence of infectious diarrhoea compared with non-pregnant population, but consequences may be more serious. Send stool cultures in any pregnant ♀ with new-onset diarrhoea, as ➲ *Salmonella* and ➲ *Campylobacter* infections associated with foetal and maternal mortality, and may indicate role for early antibiotics (see ► Approach to acute diarrhoea). *Listeria monocytogenes* infection may arise from eating unpasteurized dairy products (e.g. soft cheese), an important cause of foetal death. As well as diarrhoea, may present with early labour and flu-like symptoms. After sending blood and stool samples, empirical antibiotic treatment should be given (e.g. amoxicillin 500mg PO tds).

Inflammatory bowel disease

Patients with symptoms suggestive of undiagnosed IBD (see ➲ ulcerative colitis, ➲ Crohn's disease) during pregnancy (e.g. chronic bloody diarrhoea) require appropriate investigation (including colonoscopy, which may be performed if essential), as active IBD is linked to foetal loss. The vast majority of patients with well-controlled disease have a normal pregnancy. In patients with known IBD, steroids and 5-ASA are safe. Although azathioprine should not be started in pregnancy, there is no strong evidence for its risks during pregnancy, and most clinicians advise continuation after discussion with patient. Risk of pregnancy complications is certainly higher in those who reactivate IBD after precipitous cessation of immunosuppression. Methotrexate is contraindicated.

Increasingly patients on biologic therapy for IBD become pregnant. Infliximab and adalimumab are both IgG1 molecules, which can cross the placenta. No evidence of harm to baby in several large studies, but guidelines recommend cessation of anti-TNF in the 3rd trimester to avoid presence of anti-TNF in foetal blood and possible immunosuppression. Vaccination with rubella is contraindicated for 6mo. No firm guidelines are yet available for use of anti-integrin monoclonal antibodies, or newer agents such as ustekinumab.

Rectal bleeding

Most common cause in pregnancy is ➔ haemorrhoids, which may develop with ↑ abdominal pressure due to gravid uterus and be exacerbated by constipation. May also occur due to anal fissure or IBD.

Liver problems in pregnancy

Changes in ➢ LFTs are common during pregnancy. Depending on the pattern of derangement and clinical scenario, these range from reflecting a normal physiological response, to a potentially fatal complication necessitating urgent delivery. Normal pregnancy may be associated with development of palmar erythema and spider naevi (up to 60%), and laboratory abnormalities including ↓ serum albumin (mean 31g/L in 3rd trimester) and up to 5× ULN ↑ serum ALP (from placenta). Other LFTs, including bilirubin and transaminases, ↓ or remain normal.

Clinical assessment

- When assessing liver abnormalities in pregnant ♀, consider whether abnormalities are independent of, or related to, the pregnancy. Duration of pregnancy and presence of clinical features of liver disease may provide vital clues:
  - Have results been abnormal in past? Check with GP, pathology records.
  - Are there risk factors/clinical features to suggest pre-existing liver disease?
- Mild LFT abnormalities in asymptomatic women may be incidental findings during 1st trimester antenatal assessment (including ➲ hepatitis B serology), and may represent the 1st healthcare contact at which an underlying liver disease is identified. Further assessment and management will depend on pattern of LFTs and associated features (see ▶ Approach to well patients with abnormal liver tests). Important to make diagnosis because of possible changes in activity of chronic liver disease during pregnancy, or foetal risks (e.g. viral transmission).
- LFT derangement may occur in 50% of women with hyperemesis gravidarum (see ▶ Approach to GI problems in pregnancy), often during 1st and 2nd trimesters, with mild ↑ Bn (rarely jaundice) and liver enzymes. Usually resolves with adequate nutrition.
- Acute viral hepatitis (especially ➲ hepatitis A, B, E) most common cause of jaundice during pregnancy worldwide. Associated with higher rate of morbidity and mortality in pregnant compared with non-pregnant ♀, and important cause of foetal loss.
- Jaundice in pregnancy may be due to any cause, and requires active investigation (see ▶ Approach to recent-onset jaundice).

Effects of chronic liver disease on pregnancy

Immunological changes during pregnancy have been implicated as a cause of both deterioration (with associated clinical presentation) and improvement in liver function due to ➲ autoimmune hepatitis, ➲ primary biliary cholangitis, and ➲ primary sclerosing cholangitis. Non-cirrhotic chronic viral hepatitis rarely causes problems during pregnancy, with management mainly related to prevention of neonatal infection. Perinatal vaccination highly effective at ↓ risk of chronic HBV infection (see ➲ hepatitis B). Neonatal acquisition of ➲ hepatitis C from infected mother is ≈5%, but no vaccine is currently available, and no convincing evidence that mode of delivery (vaginal versus caesarean) affects transmission. Antiviral therapies such as tenofovir may be safely given for ➲ hepatitis B during pregnancy, but ribavirin for ➲ hepatitis C is absolutely contraindicated because of teratogenicity. Other directly acting antiviral therapies not currently recommended.

➲ Cirrhosis often leads to infertility, but where pregnancy does occur, variceal bleeding due to ➲ portal hypertension is a particular risk in the 2nd and 3rd trimesters. Prophylaxis with β-blockers should not be stopped. Although pregnancy may be successful post-➲ liver transplantation, ↑ risk of complications. OGD recommended at 20 weeks.

Pregnancy-related liver disease

Some liver diseases are unique to pregnancy, and may have life-threatening consequences. It is vital to consider these in all pregnant ♀ with symptomatic disease and LFT abnormalities, particularly in 3rd trimester. Include ➲ acute fatty liver of pregnancy (AFLP), ➲ HELLP syndrome, and ➲ obstetric cholestasis. Prompt diagnosis is crucial, as delay in delivery in AFLP and HELLP syndrome is associated with high maternal and foetal mortality.

Investigations

- Bloods. All patients require FBC, clotting, U&Es, LFTs, Glu. Other bloods tailored to specific clinical scenario, as discussed earlier (and see ▶ Approaches to well patients with abnormal liver tests, recent-onset jaundice).
- US to look for biliary obstruction, chronic liver disease with ➲ portal hypertension, fatty liver, liver haematoma, ➲ gallstones, and patency of vasculature (hepatic veins).
- Liver biopsy high risk and rarely required.

Management

- Depends entirely on diagnosis.
- Expert obstetric and hepatology advice should be sought for most cases, particularly for pregnancy-related liver disease (e.g. AFLP, HELLP), or in any patient with significant liver disease for whom intervention may be required during pregnancy (e.g. chronic ➔ hepatitis B).

Malabsorption and steatorrhoea

Malabsorption refers to defective uptake or transport of digested nutrients from the small bowel mucosa (e.g. in ➲ coeliac disease). **Maldigestion** refers to impaired breakdown of food in the gut lumen (e.g. due to pancreatic insufficiency in ➲ chronic pancreatitis, or inadequate bile in ➲ primary biliary cholangitis). In practice, 'malabsorption' usually used to cover both. There are many causes (see Box 1.20).

Steatorrhoea is the passage of bulky, pale, foul-smelling stools that float and are difficult to flush away (in fact, most stools float due to gas, not fat, content). Greasy film or even droplets of oil may be seen.

Box 1.20 Causes of malabsorption

- ➲ Pancreatic insufficiency.
- ➲ Bacterial overgrowth.
- ➲ Bile acid malabsorption.
- ➲ Whipple's disease.
- Post-▷ gastrectomy.
- Extensive small bowel resection.
- ➲ Coeliac disease.
- ➲ Tropical sprue.
- ➲ Giardiasis.
- Lactase deficiency.
- Small bowel ➲ Crohn's disease.
- ➲ Lymphoma.
- ➲ Eosinophilic gastroenteritis.
- ➲ Lymphangiectasia.
- ➲ Radiation damage (small bowel).
- ➲ Systemic mastocytosis.
- ➲ Diabetes with enteropathy.
- Thyroid disease.

Assessment

Clinical clues

- Chronic diarrhoea is a common feature in patients with malabsorption (see ▶ Approach to chronic diarrhoea).
- History of pale, bulky, terribly smelly stools that are difficult to flush suggests steatorrhoea.
- Abdominal discomfort, bloating, and flatulence common.
- Ask about symptoms related to fat-soluble vitamin (A, D, E, K) deficiency: bleeding, easy bruising, night blindness, metabolic bone

disease, low calcium/magnesium/phosphate (e.g. tetany, muscle weakness), iron (microcytic anaemia), ➲ vitamin B_{12} (macrocytic anaemia, glossitis, angular stomatitis).
- Is there a history of weight loss, failure to thrive (in children), or primary/secondary amenorrhoea?
- Does patient have a clinical problem known to predispose them to malabsorption (e.g. ➲ chronic pancreatitis, ➲ coeliac disease, small bowel ➲ Crohn's disease)?

Confirming malabsorption

- Bloods: FBC, ESR, CRP, Glucose, U&Es, LFTs, Ca^{2+}, PO^{4-}, Mg^{2+}, clotting, vitamins A, D, E, B_{12}, folate, coeliac antibodies, anti-mitochondrial antibodies.
- Stool analysis. Staining stool for fat, or quantitative measurement of fat in stool, now hardly ever used. Current approach is to measure ▷ faecal elastase as an indicator of exocrine pancreatic function (and possibly faecal α_1-antitrypsin to indicate protein malabsorption).

Identifying aetiology

- Clues to aetiology in history and initial results will lead to tests tailored to each case.
- **Endoscopy** Upper GI endoscopy with distal duodenal biopsies indicated in all patients with suspected malabsorption, unless other obvious cause. Take four duodenal biopsies to give your pathologist the best chance of a well-oriented specimen to allow proper assessment of crypt and villous architecture. Terminal ileal biopsies at ileocolonoscopy may be useful. VCE can be helpful to diagnose distal or patchy mucosal change (e.g. due to intestinal lymphangiectasia).
- **Imaging**
    - AXR may show pancreatic calcification.
    - Barium follow-through mostly replaced by MRI, although both can give useful information (e.g. strictures due to ➲ Crohn's disease, large diverticulae in ➲ systemic sclerosis, ➲ lymphoma of GI tract).
    - CT may demonstrate thickened bowel loops and lymphadenopathy, and accurately defines pancreatic anatomy (but remember that pancreatic anatomy not synonymous with function).
    - MRCP with secretin may provide some additional indication of pancreatic juice output (see ▷ pancreatic function tests).
- **Other tests:**
    - Stool microscopy and culture (including ova, cysts, parasites).
    - ▷ SeHCAT scan (see ➲ bile acid malabsorption).
    - Stool osmotic gap (see ► Approach to chronic diarrhoea).
    - Hydrogen ▷ breath tests can help with diagnosis of ➲ bacterial overgrowth.

Management

Exact treatment depends on making specific diagnosis, and treating specific disease (see 'Drugs' chapter). Where aetiology difficult to establish, therapeutic trials may further direct clinician, e.g.:

- ➲ Pancreatic enzyme supplements in suspected pancreatic insufficiency may lead to rapid improvement in steatorrhoea.
- Antibiotics may improve ➲ bacterial overgrowth.
- Bile acid sequesters (e.g. ➲ colestyramine) may improve diarrhoea/steatorrhoea related to ➲ bile acid malabsorption.
- Vitamins and other micronutrients need replacing if deficient.
- Consider effects on bone loss (see ➲ osteoporosis), so arrange ➢ bone densitometry, and provide fracture prophylaxis as necessary.
- ➲ Bacterial overgrowth may improve with surgical resection of large small bowel diverticula or strictures, but always risks exacerbating problem with further adhesions.

Mouth and swallowing problems

Problems with the mouth

Causes of a sore tongue

- Geographic tongue may be a normal variant, but also associated with atopy. May be asymptomatic or cause discomfort. Increased frequency in reactive arthritis and psoriasis (Plate 4).
- Glossitis can be caused by iron, vitamin B_{12}, or folate deficiency, and acute candida or herpetic infection (Plate 5).
- Radiotherapy and ➲ graft-versus-host disease are important causes of mucositis. Local anaesthetic mouthwashes (e.g. Difflam™) can relieve discomfort.
- Rare causes of painful tongue include diabetes and drugs (captopril).

Painful mouth ulcers

- Traumatic ulcers.
- ➲ Aphthous ulcers; 20% have associated iron, B_{12}, or folate deficiency, and potentially systemic disease (e.g. ➲ Crohn's disease).
- Malignant ulcers.

Painless mouth ulcers

Frequently innocuous and caused by dentures or cheek biting, but also:

- ➲ Lichen planus.
- Leukoplakia.
- Oral ➲ candida.
- Oral telangiectasia as part of ➲ hereditary haemorrhagic telangiectasia (see Plate 3).
- Other pigmented lesions (Addison's disease, Kaposi's sarcoma, black tongue in patients on tetracyclines, bismuth, linezolid).
- Blisters can be caused by pemphigus, pemphigoid, or drugs. Other so-called blistering disorders, such as epidermolysis bullosa and erythema multiforme, tend to cause ulcers rather than blisters.

Halitosis

Common causes:

- Dental or tonsillar abscesses.
- Gingivitis/stomatitis.
- Any cause of dry mouth (drugs, fever, dehydration, Sjögren's syndrome, radiotherapy).
- Some foods (ethanol, garlic).

Systemic disease: chronic lung pathology (bronchiectasis, lung abscess), liver failure, uraemia, and diabetic ketoacidosis (see Table 1.22).

Table 1.22 Oral manifestations of disease

Disease	Oral manifestation
Vascular disorders	
➲ Hereditary haemorrhagic telangiectasia	Telangiectasia on lips and mouth
Blue rubber bleb naevus syndrome	Dark blue soft compressible nodules
Bullous eruptions	
Epidermolysis bullosa	Mouth involvement most common in scarring (dystrophic) form
Pemphigus/pemphigoid	Oral blisters/erosions common in pemphigoid and almost universal in pemphigus
Rheumatological disorders	
➲ SLE	Oral ulcers
➲ Systemic sclerosis	Telangiectasia, microstomia (Plates 2 and 3)
➲ Behçet's disease	Oral ulcers
Miscellaneous	
➲ Amyloidosis	Small waxy amber papules on face and lips
➲ Fabry's disease	Angiokeratomas on lips and mouth
➲ Kaposi's sarcoma	Blue-red macules on oral mucosa
➲ Porphyria	Photosensitivity
➲ Pernicious anaemia	Glossitis
➲ Crohn's disease, ➲ coeliac disease	Aphthous ulceration

Evaluation and management

Ask about diet, medication, and non-oral disease. Emphasize importance of oral and dental hygiene. Routine tongue brushing and antiseptic mouthwashes can help, as can artificial saliva if xerostomia.

Mucocutaneous features of HIV (see ➲ HIV and the gut)

- >90% of HIV-infected patients have at least one oral manifestation.
- Most common HIV-associated mouth infection is *Candida* (see ➲ candidiasis). Most viral causes secondary to herpesviruses (➲ herpes simplex, ➲ cytomegalovirus, ➲ herpes zoster). Oral hairy leukoplakia seen in 40%; caused by lytic Epstein–Barr virus infection.
- Bacterial infection leading to periodontal disease is common and may progress to severe necrotizing stomatitis.
- Neoplasms: ➲ Kaposi's sarcoma and lymphoma.

Problems with swallowing

Do not confuse **dysphagia** (difficulty with act of swallowing, or of food proceeding into stomach) with **globus** (sensation of lump or something in the throat). Although globus is often functional, it can be caused by lesions in neck, pharynx, or larynx. The old term globus hystericus is now considered inappropriate—hysterical or histrionic features nearly always absent, although globus is a common somatization symptom. There is little evidence that a high pressure upper oesophageal sphincter is associated with globus sensation.

Odynophagia means pain on swallowing and suggests oesophageal inflammation or ulceration. Two common causes: medications and infections. Rarely occurs with reflux disease. Pill-induced ➔ oesophagitis usually has acute history, and careful drug history usually suggests diagnosis. Infections are more common in immunocompromised. Symptoms are non-specific but certain infections are more common in HIV (➔ *Candida*) or transplant patients (herpes or CMV).

Dysphagia: oropharyngeal and oesophageal

Difficulty with initiating swallowing is called **oropharyngeal dysphagia**. Many local, neurological, and muscular causes; the dysphagia is usually part of wider disease process and diagnosis is often straightforward (see Box 1.21). Difficulty with passage of swallowed substances down oesophagus is referred to as **oesophageal dysphagia**. Causes include motility problems or mechanical lesions (intrinsic or extrinsic to oesophagus) and are listed in Box 1.22.

Clinical evaluation

History and examination

Trouble starting swallow or transferring food from mouth into oesophagus suggests oropharyngeal dysphagia. Associated symptoms include nasal regurgitation, dysarthria, and nasal speech. May be cranial nerve abnormalities, or weakness caused by muscular disease or stroke. Careful examination of the pharynx and larynx is important.

In oesophageal dysphagia, three questions in the history are important:

- What kind of food (solid or liquid) produces symptoms? Motility disorders result in slowly progressive dysphagia for solids and liquids, while in mechanical obstruction dysphagia is worse for solids.
- Is dysphagia intermittent or progressive? Classic causes of intermittent dysphagia are ➔ Schatzki ring or some motility disorders such as diffuse oesophageal spasm.
- Is there associated heartburn?

Site of localization of limited value. In particular, dysphagia localized by the patient to neck is often referred from below.

Presenting features of clinical conditions

The various clinical conditions causing dysphagia are listed in the A–Z.

Box 1.21 Causes of oropharyngeal dysphagia

Neuromuscular diseases

Central nervous system

- Brainstem CVA.
- Parkinson's disease.
- ➲ Wilson's disease.
- Multiple sclerosis.
- Amyotrophic lateral sclerosis.
- Tabes dorsalis.

Peripheral nervous system

- Bulbar polio.
- Peripheral neuropathies (diphtheria, botulism, rabies, diabetes).

Motor endplate

- Myasthenia gravis.
- Muscular dystrophy.
- Metabolic disease (thyrotoxicosis, steroid myopathy).
- ➲ Amyloidosis, ➲ SLE.

Local structural causes

- Inflammatory (abscess, ➲ TB, syphilis).
- Neoplastic.
- ➲ Oesophageal web.
- ➲ Plummer–Vinsen syndrome.
- Extrinsic compression.
- Surgical resection.

Disorders of upper oesophageal sphincter

- Hyper- or hypotensive upper oesophageal sphincter.

Box 1.22 Causes of oesophageal dysphagia

Motility disorders

- ➲ Achalasia.
- ➲ Systemic sclerosis.
- Diffuse oesophageal spasm.
- Collagen vascular diseases.
- ➲ Trypanosomiasis/Chagas' disease.

Mechanical, intrinsic

- Peptic stricture.
- ➲ Oesophageal ring.
- ➲ Oesophageal cancer.
- Rare causes include webs, diverticula, benign tumours, oesophageal haematoma, foreign bodies (e.g. food bolus).

Mechanical, extrinsic

- Vascular compression, cervical osteoarthritis, mediastinal abnormalities.

Assessment

Although modern endoscopy with intubation under direct vision is safe in most cases, there is a risk of intubating an oesophageal pouch, which is one traditional reason for suggesting barium swallow as initial investigation. More importantly, endoscopy gives little information regarding dynamic process of swallowing. For oropharyngeal dysphagia, a video barium swallow with solid or semi-solid bolus such as marshmallow is the best test. If any evidence of an obstructing lesion, an endoscopy should be performed, with biopsy of any lesion. If endoscopy is negative or suggests a motility disorder, ➢ oesophageal manometry should be done.

Therapeutic considerations

- Oropharyngeal dysphagia caused by ➔ Parkinson's disease, hypothyroidism, myositis, and myasthenia is treatable, emphasizing the importance of making specific diagnosis.
- Dysphagia resulting from degenerative neurological disease can often be helped by a rehabilitation programme organized by speech and language therapy.
- Treatment of mechanical obstruction depends on cause but may involve surgery, dilatation, or stenting.
- Motility disorders are treated medically, and sometimes surgically.

Nausea and vomiting

Definitions and neurophysiology

The **vomiting centre** lies in the medulla, close to centres controlling respiration and salivation (hence associated hyperventilation and salivation). Receives signals from **chemoreceptor trigger zone** (located in 4th ventricle, also known as area postrema, with blood supply from posterior inferior cerebellar artery and no blood–brain barrier). This is the site of action of certain drugs causing vomiting (see Box 1.23) but also receives afferent fibres from the stomach, intestines, gallbladder, peritoneum, and heart.

- Nausea is probably mediated by similar pathways, which overlap with those mediating satiety ∴ anorexia usually accompanies nausea.
- Distinguish vomiting from regurgitation. Latter usually effortless without muscular activity involved in vomiting; associated with sour or bitter taste, and not with nausea).

Box 1.23 Drugs causing nausea and vomiting

- Via chemoreceptor trigger zone: opiates, digoxin, L-dopa, ipecacuanha, cytotoxic drugs.
- Antibiotics (tetracyclines, → METRONIDAZOLE, → ERYTHROMYCIN).
- Sulfonamides (including sulfasalazine).
- Aspirin and ➲ NSAIDs damage gastric mucosa and may stimulate the vomiting centre via ascending afferents.
- Alcohol acts directly on chemoreceptor trigger zone and via gastric mucosal damage.

Clues in reaching a diagnosis

Timing

- Early morning vomiting may be associated with pregnancy (see ► Approach to GI problems in pregnancy), ↑ intracranial pressure, uraemia, or post-gastrectomy.
- Vomiting during or soon after a meal is often psychogenic.
- Vomiting one to several hours after meal more associated with gastric stasis (➲ pyloric stenosis), upper small intestinal obstruction, gastroparesis (see ➲ diabetes and GI tract), ➲ gallstones, ➲ systemic sclerosis, or ➲ coeliac disease.

Pain

- The pain of ➲ peptic ulceration (epigastric, meal-related, causing night-time waking, not periumbilical/diffuse) is often relieved by vomiting.
- Vomiting associated with severe back pain can be caused by posterior duodenal ulcer, ➲ pancreatitis, or ➲ pancreatic cancer.
- Central colicky pain with gurgling and profuse vomiting of bile-stained fluid suggests small bowel obstruction.
- Vomiting with large bowel obstruction usually occurs late, accompanied by distension and absolute constipation.
- Think of non-GI causes. Severe pain such as ureteric colic can cause nausea and vomiting, and may be only sign of urinary infection. The same may be true of pneumonia, especially in the elderly.

Systemic symptoms and signs

Normal appetite should raise suspicion of a psychogenic cause, although can be associated with mechanical obstruction or ↑ intracranial pressure. Weight gain suggests absence of serious organic disease, but patients with ➲ peptic ulcers may put on weight because eating relieves their symptoms, and i BMI is associated with idiopathic intracranial hypertension.

Nature of vomitus

Recognizable food suggests gastric stasis. Vomiting that smells faeculent suggests small bowel obstruction, ➲ ileus, gastrocolic fistula, or ➲ bacterial overgrowth. Blood in vomit is potentially serious and may require management as for ▲ **acute upper GI bleeding** ▲, although 'coffee-ground vomiting' is non-specific, representing appearance of many different kinds of vomited particulate matter. Blood first appearing after several vomits may be due to damage around oesophagogastric junction (see ➲ Mallory–Weiss tears).

Past medical history

Details of previous surgery is important. Information on childhood health may be relevant, and ➲ gallstones, ➲ IBD, and ➲ coeliac disease can be familial.

Social factors

Information about home, marriage, job, children, and sexual problems or abuse may be relevant, particularly if no cause can be identified and if questions in these areas elicit anxiety or emotion.

Approach to investigation

- Blood tests are usually simple and based on history and examination.
  - FBC may reveal anaemia; iron deficiency may suggest peptic or malignant ulceration, or disease of the small bowel.
  - ↑ MCV may be due to alcohol excess, ➔ vitamin B_{12}, or folate deficiency.
  - U&Es may be abnormal secondary to vomiting (e.g. ↓ K^+, ↓ Na^+ hypochloraemic metabolic alkalosis), or reflect underlying primary renal dysfunction. Check calcium level and ▷ LFTs. Send ▷ amylase in acute presentation to exclude ➔ acute pancreatitis.
- Upper GI endoscopy may help, particularly to exclude peptic ulcer or other mucosal abnormalities, and bile reflux. However, endoscopy is a poor test of function and barium studies may be better in assessing upper GI stasis and obstruction.
- US liver and biliary tree to look for gallstones.

Management

- Central goal is to identify cause (Boxes 1.24 and 1.25), as this determines treatment.
- Where psychogenic factors appear important, specialist psychological input beneficial.
- Lifestyle advice, including abstinence from alcohol, may help.
- A wide range of drugs are available for nausea and vomiting. They should be used in a stepwise manner, with knowledge that all have side effects (see → ANTIEMETICS).

Box 1.24 Painless causes of vomiting

Infective

- Viral gastroenteritis.
- Food poisoning.
- ➔ *Helicobacter pylori*.
- Infections elsewhere, such as UTI or pneumonia.
- Viral labyrinthitis.

Mechanical obstruction

- Pyloric stenosis or duodenal obstruction due to ➔ gastric or ➔ pancreatic cancer.
- ➔ Oesophageal cancer.
- Biliary reflux, particularly if previous gastric surgery.

Alcoholic gastritis

- Often causes early morning retching—usually small volumes and often bloodstained.

▲ ***Acute liver failure*** ▲

Metabolic causes

- Addison's disease (look for postural hypotension, mucosal pigmentation: ↑ or normal K^+ particularly notable, since ↓ K^+ more expected after vomiting).
- Also consider hypercalcaemia, uraemia, and hyperthyroidism.
- Up to 30% of diabetic patients may have intermittent nausea or vomiting—see ➔ **Diabetes and the GI tract**.

Box 1.25 Causes of vomiting without nausea

- Intracranial tumours. Ask about headache. Full neurological exam.
- Raised intracranial pressure. Look for papilloedema.
- Intracranial infection (encephalitis/meningitis).
- Migraine.
- ➔ Cyclical vomiting syndrome.
- Cannabis use.

Non-cardiac chest pain

- Up to 30% of patients undergoing coronary angiography for acute or recurring chest pain have normal coronary arteries. A substantial proportion of these referred are to gastroenterologists for opinion.
- Major non-cardiac causes of chest pain include musculoskeletal, psychological (or psychiatric), and oesophageal disorders.
- Oesophageal distension or acid perfusion of oesophagus can produce pain, mimicking angina pectoris.

Characteristics and causes of oesophageal pain

- Can be similar to anginal pain and may be exercise related. May be triggered by hot or cold food or drink. Other oesophageal symptoms usually present (heartburn, reflux, dysphagia). Meal-related pain or pain relieved by antacids suggestive (but not diagnostic).
- Specific mechanisms are not well understood. See Table 1.23 for causes, and see ➲ oesophageal motility disorders.

Evaluating the patient with non-cardiac chest pain

- Rule out cardiac disease first. In young patients, negative ECG during pain with normal CT coronary angiogram or cardiac stress test is sufficient. In older patients, or where diagnostic uncertainty remains, direct coronary angiography remains the gold standard.
- Consider musculoskeletal causes (look for point tenderness) and psychological or psychiatric causes.
- For possible oesophageal causes, do upper GI endoscopy or barium studies. If normal, try high-dose → PPI bd for 6–8wk. 24h pH testing and oesophageal manometry may be useful.

Table 1.23 Causes of oesophageal pain

Cause	Comments
Reflux of gastric contents	Causes heartburn, but same symptoms elicited by alkaline reflux of bile salts and experimental balloon dilatation of oesophagus. Correlation between episodes of reflux and symptoms poor. 30% of patients with ➲ Barrett's oesophagus are acid insensitive.
➲ Oesophageal motility disorders	Patients with non-cardiac chest pain often have motility disorders on manometry: high-amplitude contractions or frequent simultaneous contractions.
Change in temperature or luminal distension	Hot or cold liquids or food bolus impaction can produce chest pain. Low pain threshold or visceral hypersensitivity may contribute.

Reflux as a cause of chest pain

Significant reflux occurs in 50% of patients with normal coronary arteries and chest pain, with episodes of pain coinciding with reflux on pH record. Since most patients do not have oesophagitis, **upper GI endoscopy is not a useful diagnostic test**. Barium studies can be more useful in assessing possible motility problems. A trial of high-dose PPI or 24h ambulatory pH testing are the most useful tests.

Treatment of oesophageal chest pain

- Reassurance based on diagnostic tests can sometimes help (although many patients continue to believe cardiac disease still present).
- Optimal acid suppression may involve night-time → H_2 RECEPTOR ANTAGONISTS as well as high dose → PPIs.
- Identifying reflux is important because many drugs used in attempt to relieve pain due to motility disorders (nitrates, calcium antagonists) can aggravate reflux.
- Low-dose tricyclic antidepressants (e.g. amitriptyline 10–20mg PO nocte) effective in clinical trials but should be taken for at least 2mo before maximal benefit shown. This may work by altering visceral pain thresholds.

Nutritional support

Principles of nutritional assessment

- High prevalence (20–40%) of undernutrition in patients admitted to hospital, which tends to worsen during admission.
- No gold standard for determining nutritional status. All approaches have been validated by assessing outcomes rather than nutrition-specific parameters.
- Best simple assessment is ➔ BMI.
- Serum albumin is a good predictor of surgical outcome but correlates poorly with overall nutritional status because, like many indicators of nutritional status, it is influenced by illness or injury.
- Clinicians need to recognize, assess, and treat patients with protein-energy malnutrition as well as those with specific nutrient deficiencies.

Indications for nutritional support

Patients are likely to eat more if given assistance at mealtimes and an opportunity to eat foods they like. They should be allowed to eat food brought in by friends and family, if desired.

Indications for supplemental feeding

- Oral intake is absent or likely to be absent for >5–7d (earlier instigation may be needed in malnourished patients).
- In postoperative patient unable to tolerate oral intake, consider supplemental feeding:
  - Within 1–2d if severely malnourished (BMI <16 and/or weight loss >15%).
  - Within 3–5d if moderately malnourished (BMI <18.5 and/or weight loss >10%).
  - Within 5–7d otherwise.

Use the enteral route where possible

- Enteral feeding can supply gut-preferred fuels such as glutamine and ➔ short-chain fatty acids, often absent from ➔ parenteral nutrition (PN) preparations.
- Enteral feeding can prevent mucosal atrophy, preserves mucosal and pancreatic enzyme function, and maintains GI IgA secretion.
- PN associated with complications related to line sepsis.
- Enteral feeding prevents cholelithiasis by stimulating gallbladder motility (gallstone formation is common in patients on PN, especially if little or no oral intake).
- Enteral feeding requires less frequent monitoring of electrolytes and volume status, and is less expensive to provide.

Indications for parenteral feeding

- Inadequate length of absorptive intestine: ➲ short bowel syndrome (<100cm small intestine, or <50cm small intestine if in continuity with colon).
- Intestinal obstruction (with exception of oesophageal and duodenal obstructions that can be bypassed with endoscopically placed enteral feeding tube).
- Severe mucositis (e.g. complicating chemotherapy).
- Prolonged ileus (e.g. due to severe sepsis).
- High-output enterocutaneous fistula in patients where ↓ enteral intake ↓ fistula output.
- Chronic intestinal ➲ pseudo-obstruction.

Techniques for delivering nutritional support

Enteral

Supplemental or sip feeding

Variety of ➲ oral rehydration therapies of benefit in patients with severe fluid loss, high-output enterostomies, and short bowel syndromes. Enteral nutritional support formulas can be subdivided into:

- Pre-digested feeds. Includes feeds made up of short peptides (oligomeric) and those of free amino acids (monomeric 'elemental').
- Polymeric. Feeds containing whole proteins.

Tube feeding and enterostomy feeding

Useful where patients have functioning GI tract but cannot or will not eat adequately. Many different approaches possible (e.g. nasogastric, nasojejunal, gastrostomy, jejunostomy; for practical advice, see ➢ 'Clinical practice and diagnostics', pp. 176 and 205–7). Choice of route depends on physician experience, prognosis, estimated duration of feeding, and patient preference.

Soft-bore NG tubes can stay in place for several weeks and allow eating. However, if feeding is required for >2–4wk, ➢ PEG appropriate. NJ feeding can be useful in patients with gastroparesis or ➲ pancreatitis, but does not necessarily ↓ the risk of aspiration or dislodgement. Continuous drip-feeding generally better than bolus feeding (as less likely to cause diarrhoea or reflux resulting in aspiration). If dietician not available, starting at rate of 30ml/h is appropriate (unless risk of ➲ refeeding syndrome).

Feeding enterostomies are usually inserted using ➢ PEG technique, although surgical or radiological placement are not uncommon. Jejunal feeding tube placement is possible by threading tube through existing gastrostomy (PEG with jejunal extension, PEG-J) or surgical approach.

Routine use of endoscopic gastrostomy tube insertion has revolutionized management of patients debilitated by progressive neuromuscular diseases, including stroke. Common indication is an inability to eat satisfactorily 2–4wk after the initiating event. Significant incidence of complications (see ➢ 'Clinical practice and diagnostics', p. 205), which requires informed management.

Parenteral feeding

Peripheral or central venous access

Parenteral feeding is associated with life-threatening complications unless managed optimally.

- With modern feeds, **peripheral catheters** can be used short term (up to 2wk). Thrombophlebitis related to duration of feeding and osmolarity of feed and can be minimized by careful insertion, aseptic technique, and GTN patches. **Peripherally inserted central catheters** (PICC lines) are inserted via basilic vein at antecubital fossa (avoid the cephalic vein as it joins the axillary vein at a sharp angle, which can make advancement beyond this point difficult).
- **Central venous catheters are** placed via a subcutaneous tunnel from point on the chest wall distant from point of entry of catheter into vein. Insertion via infraclavicular or low jugular routes. Catheter tip should be proximal to reflection of pericardium onto SVC, to avoid small risk of tamponade consequent to erosion of catheter through heart or lower SVC wall (can be done by checking tip no lower than 2cm below a line joining lower borders of medial ends of the clavicles on PA CXR and is true for any central venous catheter). **Always** check catheter is in lumen before commencing feed. Central catheters must be used only for feeding and not for giving drugs or taking blood. In case of a fever in a patient with central catheter, blood cultures should be taken both peripherally and centrally.

Calculating the requirements and choosing the feed

Calculate energy requirements

Calculate the **basal metabolic rate**. Energy requirements depend on weight, activity level, and underlying disease. This is historically done using Schofield charts, but a variety of websites with online calculators are now available (e.g. 🖱 www.room42.com, 🖱 www.motionworksfitness.com).

- Add 10% for each degree Celsius ↑ in temperature.
- Adjust for patient's mobility:
  - On ventilator: –15%.
  - Unconscious: ±0%.
  - Bedbound and awake: +10%.
  - Sitting in a chair: +20%.
  - Mobile on ward: +30%.
- Add up to 600kcal/d if weight gain required.

Protein

Mean requirement measured in grams of nitrogen (gN)/d is:

- 9gN/d for ♂.
- 7.5gN/d for ♀.
- 8.5gN/d for pregnant ♀.

Often in disease requirements increase: if patients are burnt, septic, or otherwise catabolic, ↑ nitrogen to usual maximum of 1gN/100kcal. Can be checked by monitoring nitrogen loss via urinary urea excretion. In general:

- In low catabolic states, nitrogen requirements = 0.16g/kg/24h.
- In intermediate catabolic states, requirements = 0.2–0.3g/kg/24h.
- In high catabolic states, requirements = 0.25–0.35g/kg/24h.

Carbohydrate

Glucose is the usual predominant energy source; required fuel for blood cells, bone marrow, and renal medulla; and the preferred fuel for the brain. Usually the infusion rate kept below 4ml/kg/min.

Fat

Lipid emulsions provide energy and a source of essential fatty acids as well as linoleic and linolenic acids. The optimal percentage of calories that should be infused as fat is not known, but at least 5% of total calories should be given as lipids to prevent fatty acid deficiency. Most complications of lipid infusion (pulmonary dysfunction, pancreatitis, hypersensitivity) occur with >1kcal/kg/h; in practice, this translates to maximum of 500–1500ml of 10% emulsion over 24h.

Electrolyte requirements

- Sodium: provide patient's weight (in kg) as mmol/24h as baseline. Add calculated losses.
- Potassium: provide weight (in kg) as mmol/24h as baseline. Add losses.
- Calcium: 5–10mmol/d.
- Magnesium: 5–10mmol/d.
- Phosphate: 10–30mmol/d.

Monitoring nutritional support

➔ **Refeeding syndrome** See relevant section in A–Z for details. Can usually be avoided by feeding for first few days at very low levels while generously supplementing and closely monitoring potassium, magnesium, calcium, and phosphate. In patients at high risk, B vitamin supplementation should be given immediately before and during first 10 days of feeding (thiamine 200–300mg PO daily, vitamin B co-strong 1–2 tablets PO tds, or IV equivalent)

Blood sugar Stressed patients may be insulin resistant. Monitor blood or urine glucose daily.

Temperature Take blood from feeding line and peripheral vein if fever is present. If clinical suspicion of line infection, stop feed until result of cultures known.

Bloods Check renal function, as well as calcium, phosphate, magnesium, and liver function at regular intervals.

Clinical applications of nutritional support

Perioperative nutritional support

Routine perioperative nutritional support should be limited to early use of sip feed supplements as oral fluids become allowed. Some evidence this ↓ postoperative complications and length of hospital stay. Parenteral feeding advised in malnourished patients or in those with unusually prolonged postoperative course.

Short bowel syndrome

A small group of patients who have lost large amounts of intestine need supplemental IV fluids and/or nutrition.

- Patients with jejunostomy and <100cm residual jejunum likely to need long-term parenteral fluid and electrolytes.
- Patients with jejunostomy and <75cm residual jejunum likely to need long-term ➲ parenteral nutrition, fluid, and electrolytes.
- Patients with a short bowel joined to colon likely to need long-term PN if <50cm jejunum remains.
- The aforementioned refers to an "adapted" bowel. IV support may be necessary during the adaptation phase with jejunostomy and <200cm remaining bowel.
- Quality of the remaining bowel is also important. If diseased, as in extensive ➲ Crohn's disease, longer lengths of bowel may be needed.

Patients with ➲ short bowel syndrome often have negative sodium balance and large GI fluid losses and need an ➲ oral rehydration solution (ORS) with higher sodium concentration than usual ORS.

The patient on ITU

Difficulty in maintaining lean body mass during critical illness means artificial feeding should not be delayed. If the patient has lost ≥10% body weight (or if BMI <20 even if not lost weight) and will not be able to eat adequately within 2d, immediate feeding is indicated. An enteral route is preferred where possible. Special attention must be paid to those nutrients most likely to need hour-to-hour manipulation. In patients with respiratory failure, excess carbon dioxide accompanying lipogenesis underlies advice not to provide excess energy in feed—especially not as glucose—if patient retaining CO_2.

Liver disease

Most important principle is to avoid giving too much sodium (aggravates fluid retention and ascites). Rarely, protein may need to be restricted in patients with ▲ **hepatic encephalopathy** ▲, although normal protein intakes often tolerated if infused slowly over 24h. Glucose infusion needed in liver failure because of failure of gluconeogenesis.

Inflammatory bowel disease

➲ *Ulcerative colitis*

Apart from avoiding lactose-containing foods because of risk of lactose intolerance in colitis, there is no evidence to support bowel rest in severe disease. Foods that may worsen diarrhoea, such as caffeine-containing drinks, should be avoided. Low fibre diet may be better tolerated, even if there is proximal faecal loading above distal colitis. PN has no value as primary therapy (unlike ➲ Crohn's disease). Indications for perioperative parenteral feeding are no different than in other patients undergoing surgery.

➲ *Crohn's disease*

- *Enteral nutrition as primary therapy*. There are considerable data from prospective randomized trials showing enteral feeding has higher efficacy than placebo as sole primary therapy. Meta-analyses fail to show equivalence with steroids (overall remission 58% compared with 80%) although may have some role in ↓ steroid requirements or facilitating weaning off steroids. Polymeric feeds are as effective as elemental feeds and tend to be more palatable. Input from dieticians needed to enhance compliance, which is the main problem with using nutrition as sole therapy. Enteral feeding more costly and compliance poorer than with pharmacotherapy. May have particular role in managing Crohn's disease in childhood because of desirability to avoid steroids and minimize growth failure due to inadequate dietary intake.
- *Parenteral nutrition in Crohn's disease*. Indicated if intestinal failure due to obstruction, fistulating disease, or extensive resection.

Acute pancreatitis

While a period of NBM may be necessary in those patients with acute ileus following ➲ acute pancreatitis, traditional approach of universal NBM is unproven dogma. Early enteral feeding (oral, NG, or NJ) may ↓ mucosal permeability and risk of endotoxaemia, lead to a ↓ in systemic inflammatory response, and maintain calorific intake during this highly catabolic state.

Obesity

Defined as ➔ BMI ≥30. Approximately 30% of UK population is obese. Obesity is well known to cause or contribute to many health problems:

- Cardiovascular. Hypertension, coronary heart disease.
- Central nervous system. Stroke, intracranial hypertension.
- GI. Cholelithiasis, non-alcoholic steatohepatitis, reflux oesophagitis.
- Respiratory. Obstructive sleep apnoea, obesity hypoventilation syndrome.
- Metabolic. Insulin resistance, type 2 diabetes, dyslipidaemia.
- Reproductive. Polycystic ovaries.
- Neoplastic. Obesity is linked to development several cancers.

Recent developments in understanding obesity

- Recognition of syndrome of insulin resistance ('metabolic syndrome') that is important in pathophysiology of ➔ non-alcoholic fatty liver disease). Syndrome includes:
  - Abdominal obesity.
  - Hypertriglyceridaemia and ↓ HDL.
  - Hyperinsulinaemia and glucose intolerance.
  - Hypertension.
  - Elevated Apo-B and plasminogen activator inhibitor-1.
- Considerable progress made in understanding neuronal and peripheral signals mediating control of appetite and eating.

Taking a history

- Include dietary history and assessment of activity.
- Screen for depression.
- Eating disorders occur in 30% of obese patients—ask about binging, purging, lack of satiety.
- Consider comorbidities, and think about causes of secondary obesity: hypothyroidism, Cushing's syndrome, insulinoma, hypothalamic disorders, polycystic ovarian syndrome, genetic syndromes such as Prader–Willi, oral contraceptive use, medication-related (Table 1.24).
- Ask about family history.

Table 1.24 Drugs associated with obesity

Drug	Mechanism
Phenothiazines	
Valproate	↑ appetite
Tricyclics	↑ appetite
Lithium	
Steroids	
Sulphonylureas	

Blood and urine tests

- Full lipid panel (fasting cholesterol, triglycerides, HDL, LDL).
- LFTs.
- Thyroid function.
- Fasting glucose and HbA1c.
- 24h urinary free cortisol.

Managing obesity

There are many ways to induce negative energy balance and short-term weight loss, but effective management involves maintaining lowered weight and minimizing risk of related chronic diseases.

Lifestyle modifications

- Weight-reducing diets (see ➔ slimming diets).
- Increasing physical activity.
- Behavioural management.
- Recognize and acknowledge how difficult making and sustaining these changes can be for patients.

Drug therapy of obesity

- Pancreatic lipase inhibitors (→ ORLISTAT) produce dose-dependent reduction in dietary fat absorption, inducing iatrogenic steatorrhoea. Supplementation of fat-soluble vitamins may be needed.
- Sibutramine (serotonin and noradrenaline reuptake inhibitor) now withdrawn in UK due to cardiovascular side effects.
- Potential future drugs. Leptin initially gave hopes of therapeutic breakthrough but in fact most obese patients are leptin resistant. As biochemical pathways controlling appetite and weight are further dissected, novel drug targets are emerging but none are yet in routine clinical use.

Surgery for obesity

See ▷ Anti-obesity (bariatric surgery), p. 182.

Post-liver transplant patients

➲ Liver transplantation has transformed the management of patients with chronic liver disease. While detailed discussion of the intricacies of managing these patients is beyond this book's remit, this chapter provides a general guide to complications that may arise on the wards or causing presentation to emergency departments.

Early surgical complications

Most of these will be detected during the immediate postoperative hospital admission.

Vascular complications

- **Arterial thrombosis.** Relates to quality of transplant vessels and vascular anastomosis, and postoperative hypercoagulable state.
  - Early thrombosis typically leads to graft ischaemia and infarction, which may cause pain, jaundice, and ↑ ALT/AST.
  - Late thrombosis more commonly causes biliary complications, particularly intrahepatic bilomas and biliary stenosis, but with preserved graft function.
  - Diagnose using US Doppler, CT, or direct angiography.
  - Acute occlusion can be thrombolysed by interventional radiologist, or surgically revascularized. If these fail, repeat transplant may be required.
  - Late occlusion can be managed by treating biliary complications.
- ➲ **Portal vein thrombosis.** Occurs in 2–3%.
  - Liver failure predominates in less common acute presentation.
  - More typically, presents late with deranged LFTs ± pain over graft.
  - Diagnose by US Doppler or contrast CT.
  - Managed with anticoagulation. ❗ There is a bleeding risk in these patients from established GI varices, which need to be treated.

Biliary complications

- **Biliary leaks and fistulae.** May arise from biliary anastomosis, damaged cystic or accessory ducts, T-tube tract (suspect if abdominal pain post-withdrawal), or incidental intrahepatic injuries. Predispose to future biliary strictures.
  - Most early leaks due to technical issues during surgery.
  - Non-anastomotic leaks should prompt consideration of vascular compromise (see 'arterial thrombosis', just mentioned).
  - If indwelling T-tube present, use this to obtain cholangiogram. Confirmed leaks can then be managed conservatively by leaving T-tube open to divert bile flow.

  - Otherwise, obtain MRCP, which may guide ERCP and bile duct stenting. Successful in >90%. Stents can be removed after 2–3mo.
- **Bilomas.** Collections of bile within abdominal cavity or hepatic parenchyma resulting from bile leaks, often following ischaemic bile duct damage.
  - Identify with US or CT.
  - Small bilomas often respond to conservative management ± bile diversion via T-tube or endoscopically placed stent (if significant ongoing extravasation).
  - Large bilomas should be drained percutaneously.
  - Surgical intervention is reserved for those patients in whom these approaches fail, or with hepatic artery thrombosis, duct-to-duct anastomotic defect too large to heal spontaneously, or peritonitis.

Haemorrhage

- Significant postoperative bleeding in up to 20%, typically within 48h of transplantation, evidenced by increasing volumes of blood in abdominal drains, haemodynamic instability, and falling Hb levels.
- Subsides in most cases with expectant management, fluid resuscitation, and blood product support.
- Re-operation needed in 10–15%, but the source of bleeding is only found in ≈50% of these patients.

Rejection

May be hyperacute (within 24h), acute (1–2wk), or chronic (years).

- **Hyperacute** Rare nowadays with better donor–recipient immunological matching. Caused by pre-existing antibodies and complement activation where mismatch. Massive hepatocyte necrosis necessitates urgent re-transplantation.
- **Early acute** Occurs in 30–70% of patients and, when recognized, does not prejudice graft or patient survival.
  - Often clinically silent, but may present with malaise and RUQ discomfort. Consider diagnosis in any transplant recipient whose ALT/AST are rising, particularly if subtherapeutic plasma concentrations of immunosuppressive drugs.
  - Liver biopsy mandatory to confirm diagnosis.
  - Treatment involves escalation of immunosuppression, to which response is usually rapid. May include ↑ doses of 1st line agents, switching to more potent drugs, introducing additional agents (e.g. mycophenolate mofetil or antithymocyte globulin), or pulsed IV methylprednisolone (e.g. 1g IV od for 3d).
- **Late acute** Occurs after 180d, and arises in 25% patients. Of these, ~¾ respond to pulsed IV steroids and ↑ immunosuppression.
- **Chronic** Occurs after years. Characterized by progressive bile duct loss ('vanishing bile duct syndrome'), obliterative angiopathy, hepatic fibrosis, and cholestasis. Occurs in 5%.
  - More common in those with previous recurrent episodes of acute rejection, or ➔ cytomegalovirus or ➔ hepatitis C infection.

- Diagnosis suggested by derangement of LFTs (particularly Bn and ALP) several years after transplant.
- Major cause of graft failure at this time. Loss of synthetic function may not be evident until very late.
- Adjustment of immunosuppression delays progression, but eventual graft failure requiring re-transplantation is usual.

Infection

Transplant patients are predisposed to bacterial, viral, and fungal infections. Risk varies according to duration since surgery and degree of immunosuppression. Immunosuppression also often attenuates classic symptoms and signs of infection, and therefore a high index of suspicion is required. ❗ Also beware drug–drug interactions between antimicrobials and immunosuppressive agents. Infections may derive from:

- Donor liver.
- Transfused blood products.
- Exogenous organisms.
- Endogenous flora.
- Reactivation of latent infection.

Early postoperative infections

During the 1st month after transplant, nosocomial and endogenous bacterial infections predominate, including:

- Wound infections.
- Intrahepatic abscesses (associated with ischaemia).
- Extrahepatic abscesses (superinfection of haematomas and bilomas).
- Peritonitis.
- ➔ Cholangitis.
- Nosocomial pneumonias.
- ➔ *C. difficile*-associated diarrhoea.

Opportunistic infections

Infections related to immunosuppression arise from week 4 post-transplant, until profound immunosuppression is no longer required. May also emerge when prophylaxis is stopped, or if immunosuppression re-escalated to treat late rejection. Viral infection is most frequent, followed by fungi/yeast, and bacteria. After 6mo, levels of immunosuppression have usually reduced, and therefore standard community-acquired infections again predominate (although at ↑ frequency). In the absence of a clear septic focus, initial assessment should include:

- Blood cultures, including fungal cultures.
- Blood serology and PCR to CMV.
- CXR.
- Urine MC&S.
- US or CT abdomen to look for collection.

When selecting antimicrobial therapies, be aware of cytochrome P450 interactions, as these will impact plasma levels of immunosuppressants (particularly ciclosporin and tacrolimus).

➲ Cytomegalovirus (CMV)

- Most frequently isolated opportunistic pathogen.
- May be primary infection from liver or blood donor into seronegative recipient, or reactivation of endogenous latent infection.
- Presents with fever, malaise, and peripheral blood lymphocytosis with atypia on blood film.
- Hepatitis manifests with ↑ ALT/AST, ↑ Bn, and pain over graft.
- Can also develop pneumonitis and CMV colitis.
- Diagnosis principally through PCR quantification of viraemia and biopsy of affected organ. Histology may show pathognomonic inclusion bodies, but these have limited sensitivity. Immunohistochemistry or *in situ* hybridization ↑ yield.
- Treat with → GANCICLOVIR 5mg/kg IV bd or valganciclovir 900mg PO bd. Duration guided by clinical response and suppression of viraemia. Monitor U&E for nephrotoxicity, and FBC for myelosuppression.
- For patients at high risk of developing CMV (donor-positive, recipient-negative transplants; high blood transfusion requirements; immunological rejection with escalating immunosuppression), prophylaxis with valganciclovir 900mg PO od can be provided.

Epstein–Barr virus (EBV)

- Frequently reactivated latent infection.
- Clinical presentation similar to CMV, although pneumonitis and colitis much less common. Risk factor for post-transplant lymphoproliferative disease (see p. 114).
- Diagnosis serological, with viral load quantitated by PCR.
- Treatment with → ACICLOVIR 5mg/kg IV qds for severe disease, or 800mg PO 5/d for mild-to-moderate infections.

Other viruses

Common pathogens include ➲ adenovirus, ➲ herpes simplex virus, varicella zoster virus, ➲ hepatitis B & ➲ hepatitis C.

Pneumocystis jirovecii

- *Pneumocystis jirovecii* pneumonia (PCP) presents insidiously with progressive exertional dyspnoea, fever, and non-productive cough.
- Patients hypoxic, or desaturate rapidly on exertion.
- Respiratory examination can be remarkably normal given degree of hypoxia.
- Classic CXR appearance said to be diffuse bilateral infiltrates extending from both hila, but may be normal of asymmetric. Substantial overlap between appearances of PCP and bacterial pneumonia.
- Organism can be identified on microscopy of induced sputum or bronchoalveolar lavage (expectorated sputum has low sensitivity). Inform laboratory that PCP is suspected.
- Antibiotic therapy should be commenced with co-trimoxazole 120mg/kg PO or IV in 2–4 daily divided doses for 14d. Give adjunctive corticosteroids (prednisolone 50–80mg PO od for 5d, then taper over 2wk) to patients with pO_2 <9kPa on air.
- Prophylaxis in high-risk patients should be provided: co-trimoxazole 960mg PO 3/wk virtually eliminates risk.

Other fungi

- May cause localized or disseminated infection.
- Identified on specific cultures. Include ➲ *Candida* (most common), *Aspergillus* (20%), and *Cryptococcus*.
- Treat with liposomal amphotericin (AmBisome®) 1mg/kg IV od (can ↑ to 3–5mg/kg od if limited response). Caspofungin 70mg IV on d1, then by 50mg IV od is 2nd line. Duration guided by clinical response.
- Fluconazole prophylaxis can be given to those at risk.

Chronic biliary complications

Biliary strictures

- Occur in 15% patients with long-term follow-up. Most arise within 12mo at, or just proximal to, anastomosis, usually due to postoperative ischaemia with fibrotic tissue repair.
- Formation insidious, and most frequently detected during investigation of deranged LFTs in asymptomatic patient (although ➲ cholangitis) can be presenting event.
- Absence of duct dilatation on US does not exclude stricture in transplanted liver, so MRCP or ERCP required.
- *Anastomotic strictures:*
  - Early strictures respond well to balloon dilatation and insertion of temporary stent (may require 2–3 attempts but typically remain patent long-term).
  - Late strictures (>6mo) often respond transiently to dilatation but frequently require repeat procedures, and in some cases surgical revision to ➢ Roux-en-Y necessary.
- *Non-anastomotic strictures*:
  - Occur in 10%, and risk factors include postoperative ischaemia, DCD grafts, CMV, immunological mismatch causing vasculitis, and pre-transplantation diagnosis of ➲ primary sclerosing cholangitis.
  - Balloon dilatation and stenting should be attempted, but only 50% respond.
  - Surgical revision required in many cases.
  - Diffuse disease of intrahepatic ducts should prompt consideration of early re-transplantation. Most frequently seen following non-heart beating donation where warm ischaemia selectively prejudices bile ducts.

Biliary stone disease and cholangitis

- Biliary obstruction can occur from strictures, stones, casts, or sludge.
- Clinical picture varies from asymptomatic ↑ in Bn/ALP to septic shock due to bacterial ➲ cholangitis.
- Symptoms often non-specific, and RUQ pain typical of biliary disorders in non-transplant patients are usually absent due to hepatic denervation.
- Obstruction treated endoscopically with sphincterotomy ± stent.
- Broad-spectrum antibiotics and IV fluid support are required if infection (see ➲ cholangitis).
- → URSODEOXYCHOLIC ACID delays new stone formation.

Sphincter of Oddi dysfunction

- Complicates 2–7% patients with duct-to-duct anastomosis, probably due to denervation.
- Diagnosis usually based on clinical presentation and response to sphincterotomy. Improvement in LFTs if an indwelling T-tube is unclamped, or delayed drainage of contrast at cholangiography/ ➔ HIDA scan are also suggestive. Usual treatment ERCP with sphincterotomy ± stent.

Mucocoele

- Collection of mucus from cells lining cystic duct remnants. Rare.
- Expand over weeks to years, compressing adjacent bile duct.
- CT or US show fluid collection in porta hepatis. Differential diagnosis: hepatic artery pseudoaneurysm, biloma, loculated ascites, abscess, liquefied haematoma, tumour, or adenopathy.
- Surgical excision/drainage curative.

Medication side effects

Most patients receive three immunosuppressants in the immediate post-transplant period: typically a calcineurin inhibitor (→ CICLOSPORIN/ → TACROLIMUS), mycophenolate mofetil, or → AZATHIOPRINE, and a glucocorticoid. Usually only the calcineurin inhibitor is needed beyond 6mo. Relevant side effects include:

- **Ciclosporin** Acute nephrotoxicity (40–70%, dose-related and usually reversible with dose reduction), chronic nephrotoxicity (often irreversible), hyperkalaemia, hypomagnesaemia (↑ urinary loss, supplementation often required), hypertension, venous thrombosis, tremor, headache, paraesthesia, gout, gingival hyperplasia. Dosing based on plasma drug levels and renal function (target levels derived by various centres, and based principally on clinical experience. Generally 2h post-dose levels most reflective of immunosuppression). Micro-emulsified formulations (e.g. Neoral®) provide more consistent blood levels.
- **Tacrolimus** Nephrotoxicity and electrolyte disturbance (similar to ciclosporin). Compared to ciclosporin, hypertension and hyperlipidaemia are less common, but rates of diabetes mellitus and neurotoxicity are higher. Graft and patient survival comparable, but steroid requirements lower.
- **Sirolimus** Myelosuppression, hyperlipidaemia, peripheral oedema, delayed wound healing. Structurally related to tacrolimus but inhibits IL-2 not calcineurin. Dosing more complex: serum levels require 3–5d to equilibrate and often only measured by specialist laboratories. Used in place of calcineurin inhibitors if renal toxicity.
- **Corticosteroids** Hypertension, diabetes mellitus, dyslipidaemia, cataracts, weight gain, infection, depression/mania, osteoporosis, pancreatitis, proximal myopathy, avascular necrosis, adrenal axis suppression.

- **Azathioprine** Myelosuppression, nausea, vomiting, pancreatitis, hepatotoxicity. Monitoring measures available to limit toxicity (see Section 2, ➲ AZATHIOPRINE).
- **Mycophenolate mofetil (MMF)** Neutropaenia (although less myelosuppressive than azathioprine), GI symptoms, teratogenic.

Secondary malignancy

Arises in 5–15% of patients following solid organ transplant, with risk proportional to duration and intensity of immunosuppression. ➲ Kaposi sarcoma occurs earliest (but least common), followed by lymphoproliferative disease/lymphoma, and squamous cell carcinomas appearing after 1y. Other malignancies also more frequent (e.g. GI and oropharyngeal), so patients should receive intermittent screening (e.g. skin exam, mammography, Pap smear, prostate-specific antigen (PSA), colonoscopy).

➲ Kaposi sarcoma

- Typically presents with multifocal cutaneous and visceral lesions, which usually appear as purple/red-brown papules or plaques.
- Reducing immunosuppression, or switch to sirolimus, can induce regression.
- If unsuccessful, subsequent treatment often involves combination of surgical excision, chemotherapy, and radiotherapy.

Post-transplant lymphoproliferative disease (PTLD)

- EBV-driven proliferation of B cells. Range from polyclonal hyperplasia to aggressive non-Hodgkin ➲ lymphoma.
- Monitoring EBV viral load predicts emergence of PTLD and should prompt search for developing tumour, though only 50% specific.
- Withdrawal or reduction of immunosuppression in patients with premalignant disease may be effective, as are antiviral therapies such as interferon-α, IVIG, or acyclovir. Response should be seen in 2–4wk. ↑ LDH, organ dysfunction, multiorgan involvement, and monoclonal disease predict failure of this approach.
- Localized disease has been successfully treated with surgery or radiotherapy.
- Disseminated malignancy requires chemotherapy ± B cell depletion with monoclonal antibodies such as rituximab.

Squamous cell carcinoma (SCC)

- Can affect multiple organs, with skin the most frequent.
- Perianal and vulval SCC also common.
- Oropharyngeal carcinoma more prevalent in patients transplanted for alcoholic cirrhosis.
- Reduction in immunosuppression may delay progression.
- Treatment is principally surgical, although topical therapies are available for cutaneous lesions.
- HPV vaccination preventative.

Disease recurrence

- Most pre-existing conditions other than congenital anomalies and metabolic disease recur post-transplant (e.g. ➔ primary sclerosing cholangitis).
- ➔ Hepatitis B re-infection may be prevented/limited with combination of hepatitis B immunoglobulin (HBIg) and one or more nucleos(t)ide analogues (e.g. tenofovir, entecavir—see ➔ hepatitis B).
- Graft re-infection with ➔ hepatitis C is historically universal, and may lead to accelerated cirrhosis and graft loss; however, with advent of new antiviral drugs, the chances of recurrence are low if transplant is performed when viral load is undetectable, and minimal if SVR.
- Up to 30% of patients transplanted for ➔ alcoholic liver disease return to drinking.

Recent-onset jaundice

Background

- Jaundice is yellow pigmentation of the sclerae due to subcutaneous deposition of bilirubin (Bn). Usually detectable when Bn >60µmol/L. It may be due to either ↑ production or ↓ hepatobiliary excretion.
- In assessment of patients with recent onset of jaundice, four questions need to be answered:
  - What type of jaundice is present?
  - What is the causative agent or process?
  - If due to liver damage, is jaundice a result of acute or acute-on-chronic liver disease?
  - Is there evidence of liver failure?

Type of jaundice

On the basis of history, examination, and routine biochemical tests (see Fig. 1.9), usually possible to categorize jaundiced patient into 1 of 3 disease groups.

Disorders of bilirubin production/metabolism ('pre-hepatic')

Usually asymptomatic unconjugated hyperbilirubinaemia, with few physical findings and normal transaminases (ALT/AST) and cholestatic liver tests (ALP/γGT). See Box 1.26.

Liver disease ('hepatic')

- Conjugated hyperbilirubinaemia. See Box 1.27.
- In chronic liver disease, jaundice may present with other evidence of decompensation (e.g. ascites, variceal bleeding, ▲ **hepatic encephalopathy** ▲). Acute liver injury more commonly presents with abdominal discomfort and clinical hepatomegaly.
- Wide variability of LFTs can be seen, depending on cause of liver injury. Serum ALT >1,000U/L unusual for ➲ alcoholic liver disease or ➲ autoimmune hepatitis, and suggests acute liver injury due to viruses (e.g. ➲ hepatitis A, B, E), ischaemia (?recent hypotension, atrial fibrillation), or drugs (e.g. ➲ paracetamol overdose).
- In absence of cause for new-onset jaundice, it may be clinically difficult to distinguish acute from acute-on-chronic disease. Poor/failing hepatic function not indicated by elevation of liver enzymes, but most reliably by ↑ bilirubin, ↓ albumin, ↑ prothrombin time/INR. ↑ ALP/γGT in absence of biliary dilatation suggests intrahepatic cholestasis due to range of causes (e.g. ➲ primary biliary cholangitis, drugs, TB, lymphoma).
- Liver biopsy may be required.

Biliary obstruction ('post-hepatic')

- Conjugated hyperbilirubinaemia. See Box 1.28.
- Jaundice is often associated with pruritus because subcutaneous deposition of bile acids is extremely irritant. Abdominal pain and nausea are associated with bile duct stones, and progressive painless jaundice with malignant obstruction, but history often imprecise.
- ↑ ALP/γGT classically seen in patients with ➔ biliary stricture, but associated marked ↑ transaminases characteristically may occur with biliary obstruction due to stones (➔ choledocholithiasis).

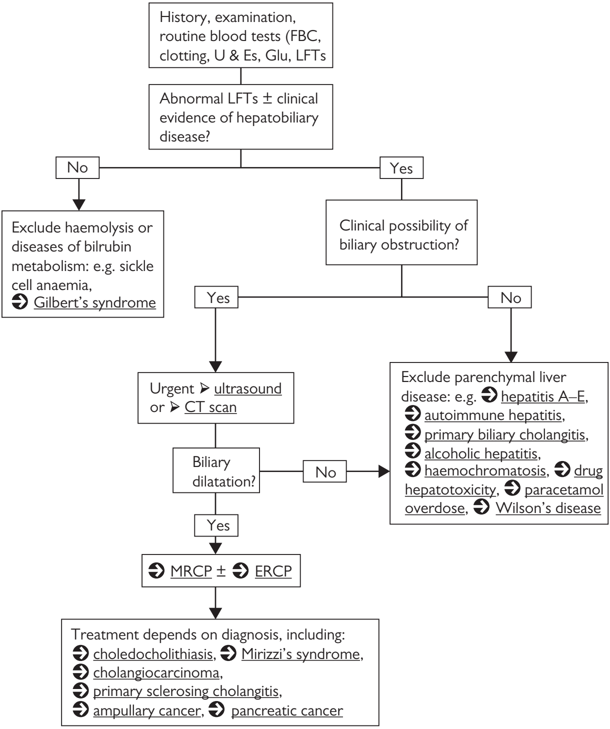

History, examination, routine blood tests (FBC, clotting, U & Es, Glu, LFTs
Abnormal LFTs ± clinical evidence of hepatobiliary disease?
No
Yes
Exclude haemolysis or diseases of bilrubin metabolism: e.g. sickle cell anaemia, ➔ Gilbert's syndrome
Clinical possibility of biliary obstruction?
Yes
No
Urgent ▷ ultrasound or ▷ CT scan
Exclude parenchymal liver disease: e.g. ➔ hepatitis A–E, ➔ autoimmune hepatitis, ➔ primary biliary cholangitis, ➔ alcoholic hepatitis, ➔ haemochromatosis, ➔ drug hepatotoxicity, ➔ paracetamol overdose, ➔ Wilson's disease
Biliary dilatation?
No
Yes
➔ MRCP ± ➔ ERCP
Treatment depends on diagnosis, including: ➔ choledocholithiasis, ➔ Mirizzi's syndrome, ➔ cholangiocarcinoma, ➔ primary sclerosing cholangitis, ➔ ampullary cancer, ➔ pancreatic cancer

Fig. 1.9 Clinical approach to recent-onset jaundice.

Box 1.26 Causes of unconjugated (indirect) hyperbilirubinaemia

- Hereditary haemolysis (e.g. ➲ sickle cell anaemia, hereditary spherocytosis).
- Acquired haemolysis (e.g. transfusion reaction, malaria).
- Defective conjugation:
  - ➲ Gilbert's syndrome.
  - ➲ Crigler-Najjar syndrome.

Box 1.27 Causes of hepatic jaundice (conjugated/direct ↑ Bn)

- Infection:
  - ➲ Hepatitis A-E.
  - ➲ Herpes simplex virus (HSV).
  - Epstein–Barr virus (EBV).
  - ➲ Cytomegalovirus (CMV).
  - Bacterial sepsis.
  - ➲ Leptospirosis.
- ➲ Alcoholic liver disease.
- ➲ Non-alcoholic fatty liver disease (NAFLD).
- ➲ Drug-induced liver injury, including ➲ paracetamol overdose.
- Ischaemia (hypotension, arterial/venous thrombosis, emboli).
- Metabolic:
  - ➲ Haemochromatosis.
  - ➲ Wilson's disease.
  - ➲ α_1-antitrypsin deficiency.
- ➲ Autoimmune hepatitis.
- ➲ Primary biliary cholangitis (PBC).
- Granulomatous liver disease (see ➲ hepatic granulomas).
- ➲ Budd–Chiari syndrome.
- ➲ Sinusoidal obstruction syndrome.
- Pregnancy-related liver disease (see ► Approach to liver problems in pregnancy).
- Malignant infiltration.
- ➲ Graft-versus-host disease.
- Impaired bilirubin excretion:
  - ➲ Dubin–Johnson syndrome.
  - ➲ Rotor syndrome.

Box 1.28 Causes of biliary obstruction (conjugated/direct ↑Bn)

- ➲ Choledocholithiasis.
- ➲ Primary sclerosing cholangitis (PSC).
- Intrinsic ➲ biliary stricture (e.g. ischaemic, traumatic).
- ➲ HIV cholangiopathy.
- Biliary infestation (e.g. ➲ *Clonorchis*).
- ➲ Pancreatic cancer.
- ➲ Cholangiocarcinoma.
- Extrinsic compression (e.g. aneurysm, hilar nodes).
- ➲ Pancreatic pseudocyst.

Clinical assessment

History

Determine onset of jaundice, associated symptoms (prodrome, abdominal pain, weight loss?), previous illnesses (autoimmunity?), alcohol intake (amount, type, duration, pattern of drinking), needle exposure (IV drugs, tattoo, transfusions?), drug history (recreational, prescription, over-the-counter, herbal remedies, drug chart?), travel and vaccination history, occupational risks (e.g. health staff, publican?), sexual history, family history.

Examination

Look for:

- Hints to cause of jaundice: smells of alcohol, needle marks, self-harm scars.
- Evidence of chronic liver disease: clubbing, Dupuytren's contracture, leukonychia, xanthelasma, Kayser–Fleischer rings, gynaecomastia, multiple spider naevi, testicular atrophy, splenomegaly, dilated superficial veins on abdomen.
- Evidence of ▲ **acute liver failure** ▲ or ▲ **hepatic encephalopathy** ▲: liver flap, confusion/drowsiness/coma, bruising, ascites, oedema.
- Observation chart—low BP?

Investigations

Blood tests

May be tailored according to clinical setting, but likely to include:

- **Viruses**. ➲ Hepatitis A (α-HAV IgM, IgG), ➲ hepatitis B (HBsAg, α-HBc IgM, IgG, HBeAg, α-HBe, and HBV DNA if HBsAg$^+$), ➲ hepatitis C (α-HCV, HCV RNA), ➲ hepatitis E (α-HEV IgM, IgG, and HEV RNA), Epstein–Barr virus (α-EBV IgM, IgG), ➲ cytomegalovirus (α-CMV IgM, IgG), ➲ herpes simplex virus (α-HSV IgM, IgG).
- **Metabolic diseases**. ➲ Haemochromatosis (serum iron, TIBC, ferritin), ➲ Wilson's disease (serum copper, caeruloplasmin, 24h urinary copper), ➲ α_1-antitrypsin deficiency (α_1-antitrypsin).
- **Drug toxicity** including random blood alcohol level, ➲ paracetamol levels, and urine for toxins.
- **Autoimmune liver disease** ➲ Autoimmune hepatitis, ➲ primary biliary cholangitis (immunoglobulins, ANA, α-smooth muscle Ab, α-mitochondrial Ab, α-LKM1 Ab).
- Initial screen for disorders of bilirubin metabolism may include measurement of conjugated and unconjugated bilirubin. Although unconjugated hyperbilirubinaemia classically seen in ➲ Gilbert's syndrome, mixed conjugated/unconjugated is usually seen and measurement useful only on occasion.
- Haemolysis assessed by FBC + film, reticulocytes, and haptoglobin.
- Culture of blood, urine, and ascites may be relevant, as may *Leptospira* serology for suspected ➲ leptospirosis.
- Tests to define degree of liver function impairment and associated disease include FBC + film, clotting profile (PT, INR, APPT), U&Es, venous bicarbonate, LFT screen, glucose.
- Markers of impaired synthetic liver function, as mentioned, and which may be seen in liver failure include ↑ serum bilirubin, ↓ albumin, ↑ PT/INR, ↓ bicarbonate/pH.

Imaging

Indicated in all cases.

- Abdominal ➢ US easily available, with 91% sensitivity and 95% specificity for biliary obstruction. Allows identification of mass lesions; exclusion of ➲ portal vein thrombosis, hepatic vein thrombosis (➲ Budd–Chiari syndrome), and hepatic arterial impairment; can provide evidence of ➲ portal hypertension; and demonstrate liver texture (?cirrhotic, fatty infiltration), ascites, and splenomegaly.
- CT of comparable use but radiation exposure + IV contrast to define vessels may be nephrotoxic, particularly in patients with associated renal injury (e.g. ➲ hepatorenal syndrome). May delineate signs of portal hypertension and mass lesions in liver.

➢ *Liver biopsy*

Rarely required in initial assessment of recent-onset jaundice. Its two roles are as an aid to diagnosis where no cause for jaundice secondary to parenchymal liver injury can be found, and in patients with proven cause in whom grade (degree of inflammation) and stage (degree of fibrosis) of liver injury histologically will affect management (e.g. alcoholic hepatitis in patient with established cirrhosis). In patients with coagulopathy (e.g. INR >1.5, platelet count $<50\times10^9$/L), a transjugular approach may be required.

Management

- Effective management is wholly dependent on prompt identification of the cause and severity of any liver disease, as specific treatment depends on type of jaundice, aetiology, and whether liver failure present.
- In patients with evidence of biliary disease on initial assessment and imaging, non-invasive modalities should be used for further investigation (e.g. MRI/MRCP), unless high clinical suspicion of large duct obstruction based on initial imaging (e.g. biliary stricture, common bile duct stones), in which case ERCP should be planned.
- See A–Z entries for management of specific conditions.

Unintentional weight loss

Background

- Unexplained unintentional weight loss is a common reason for referral to gastroenterology clinic. It often provides an interesting diagnostic challenge, not least because of the huge range of causes (see Table 1.25), and need for careful history and examination.
- Weight loss not the same as low weight; a patient whose ➔ BMI has unintentionally fallen from 30 to 20 in 2 months requires as intensive investigation as a patient who is obviously malnourished.

Table 1.25 Causes of unintentional weight loss

Occult malignancy, especially ➔ pancreatic cancer, ➔ gastric cancer	Chronic inflammatory disease (e.g. ➔ Crohn's disease)
Hyperthyroidism	Depression
Severe cardiorespiratory disease, e.g. 'cardiac cachexia', end-stage chronic obstructive airway disease	Chronic infection (e.g. ➔ TB, abdominal abscess, subacute bacterial endocarditis)
Malabsorption, e.g. ➔ chronic pancreatitis, ➔ Whipple's disease, ➔ coeliac disease	Autoimmune disease (e.g. ➔ systemic lupus erythematosus, ➔ rheumatoid arthritis)
Swallowing difficulties, e.g. oesophageal stricture	Endocrine disease (e.g. Addison's) ➔ diabetes mellitus
➔ Anorexia nervosa	Neuromuscular disease/dementia
Chronic liver disease, especially in alcoholics with malnutrition	Starvation/malnutrition
➔ HIV with immune compromise	

History

Careful history may make diagnosis.

- **How much weight** has been lost, and over what period of time? Is there **evidence** (e.g. weight chart, photos, change in dress size)?
- Clarify patient has not been intending to lose weight, and take dietary history.
- Is there a problem with perceived **body image** suggesting ➔ anorexia nervosa? Patients with this will rarely seek out help to gain weight, but may well be encouraged to attend by concerned relatives, and the psychiatric nature of this condition often results in significant deception surrounding eating habits.
- Is appetite good, or is the patient anorexic ('off their food'—often seen in malignancy)?

- Is the patient depressed (explore recent life changes, e.g. bereavement, social isolation, redundancy)?
- Have other clinical problems recently worsened, explaining weight loss (e.g. severe chronic obstructive airway disease)?
- Ask about swallowing (see ▶ Approach to mouth and swallowing) and chest symptoms (?TB, lung cancer).
- Is there any history of fever?
- Are there any areas of pain or discomfort?
- What about their bowels? Change in bowel habit may suggest ➲ colon cancer or ➲ Crohn's disease. Steatorrhoea suggests malabsorption (e.g. ➲ chronic pancreatitis).
- Are there any risk factors for ➲ HIV, or history of AIDS-defining illnesses (HIV wasting disease was historically known as 'slim disease' in Africa).

Examination

Careful examination essential (see ▹ 'Gastrointestinal examination', p. 130).

- Does patient look thin and unwell? Dishevelled patient with poor dentition may have malnutrition (e.g. associated with ➲ alcohol dependency). Are their clothes obviously loose-fitting (change in belt notch is a good clue)?
- Look for signs of hyperthyroidism (agitated, warm palms, palmar erythema, fine tremor, tachycardia, goitre).
- Splinter haemorrhages suggest subacute bacterial endocarditis.
- Fine lanugo hair on face may suggest ➲ anorexia nervosa.
- Look for lymphadenopathy, and carefully exclude a heart murmur.
- Exclude abdominal masses (but abdominal imaging will be necessary, as certain organs, such as pancreas, poorly identified on physical examination).
- Perform a rectal examination (?large prostate, low rectal lesion).
- Test urine for blood, glucose, and white cells.
- Don't forget to **weigh the patient** (surprising how often this is forgotten, but provides invaluable evidence for subsequent review). Calculate ➲ BMI.

Investigations

Focused tests will be guided by findings on history and examination. In patients with significant weight loss, but no obvious cause, non-invasive investigations may give clues to aetiology:

- Bloods: FBC, ESR, CRP, U&Es, LFTs, glucose, autoantibodies (e.g. rheumatoid factor, antinuclear antibodies), iron studies, vitamin B_{12} levels, folate, coeliac antibodies, thyroid function tests. Serum tumour markers rarely of use in absence of specific clues, but consider PSA in elderly ♂ with weight loss.
- CXR.
- Abdominal US/CT scan.

- Invasive tests (e.g. endoscopy, colonoscopy) may be needed where there is a high clinical suspicion of upper or lower GI malignancy (e.g. iron deficiency in setting of weight loss), but rarely indicated as 1st line investigations, in absence of other indicators.
- Associated pyrexia of unknown origin (PUO) requires multiple blood cultures from different sites, urine culture, and echocardiogram (even in absence of murmur). Consider CT-PET if not diagnostic.

Management

- Entirely dependent on making diagnosis as to cause of weight loss.
- In patient with no obvious cause and normal initial investigations, re-assessment, and re-weighing in 4–6wk very useful strategy. Not uncommon for no ongoing weight loss to be demonstrated, despite patient's perception to contrary. This hard evidence may allow further invasive tests to be avoided, reassurance to be given, and other patient issues to be addressed. Conversely, documented ongoing weight loss necessitates more intensive investigations.

Well patients with abnormal liver tests

Wide availability of automated biochemical analysis of blood has resulted in increasing identification of abnormal ➲ LFTs in otherwise apparently well patients. For example, 50% of patients with PBC now identified while asymptomatic. In addition, the introduction of statins for cardiovascular disease and risk modification led to increased LFT monitoring in this large population of patients, and led to the widespread recognition of ➲ NAFLD.

The clinical skill is in:

- Identifying cause without employing analysis of all possible aetiologies of liver injury.
- Defining the extent of underlying liver disease.
- Identifying those who need to be exposed to risk of ➢ liver biopsy.
- Deciding who needs long-term follow-up or treatment.

Virtually any cause of liver disease or biliary obstruction (see ▶ Approach to recent-onset jaundice) may present in asymptomatic phase, and so usual rules of making a diagnosis apply.

History

- Alcohol.
- Drugs: recreational, prescription, over-the-counter, herbal remedies. Review the drug chart—can derangement of LFTs be correlated with their introduction?
- Risks for viral hepatitis (blood transfusions, IV drug misuse, sexual contacts).
- Autoimmune diseases (e.g. thyroid disease).
- Family history.
- Other medical problems (e.g. diabetes mellitus, ➲ IBD).

Examination

Patient may be asymptomatic, but full examination essential. Is there hepatomegaly? Are there signs of chronic liver disease (e.g. palmar erythema, clubbing, spider naevi; see ➢ gastrointestinal examination, p.130), and of extent of liver injury (e.g. splenomegaly, ascites)? Hints to aetiology (e.g. obesity, needle marks, tattoos, xanthelasma)?

Investigation and management approach

What is the pattern of LFT derangement?

- Hepatitic picture (i.e. ↑ ALT/AST) may suggest chronic ➲ hepatitis B or ➲ C, ➲ NAFLD, ➲ alcohol liver disease, or ➲ autoimmune hepatitis. See Fig. 1.10.
  - ALT>AST suggests NAFLD or viral hepatitis.
  - AST>ALT more characteristic of ➲ alcoholic liver disease (especially if ↑ γGT, MCV).
  - Remember to consider other sources of ALT/AST (e.g. striated muscle— suggested by raised creatine kinase).
- Cholestatic picture (i.e. ↑ ALP/γGT) may point towards ➲ primary biliary cholangitis (PBC), ➲ primary sclerosing cholangitis (PSC), or ➲ hepatic granulomas. Also necessitates exclusion of large duct biliary obstruction (e.g. ➲ biliary stricture, ➲ pancreatic cancer) and liver metastases. Consider extrahepatic source of ALP, such as bone (especially if isolated rise and γGT normal). See Fig. 1.11.
- Isolated ↑ γGT frequent finding with automated blood analysis. May occur due to alcohol excess, drugs (e.g. steroids, anticonvulsants, statins), or fatty liver. Invasive extensive investigation rarely yields significant pathology. Patients should have tests repeated few months later, and investigated further only if additional biochemical abnormalities, significantly ↑ γGT, or new clinical problem.
- Abdominal ➢ US should be performed in all cases. Heterogeneous fatty infiltration consistent with NAFLD.
- Further imaging (e.g. CT, ERCP, MRCP) may be necessary, depending on US findings.
- ➢ Liver biopsy should be considered if no cause identified and LFTs remain abnormal over 6–12mo (e.g. >2× ULN), and despite initial interventions. May also be needed to define degree of liver injury where cause identified (e.g. viral hepatitis, ➲ alcoholic liver disease).

If all these tests are negative and LFT derangement persists, consider undeclared alcohol excess, coeliac disease, glycogen storage disease, Addison's disease, and α_1-antitrypsin deficiency.

Treatment

Treatment depends on diagnosis. However, if no clear cause can be identified and patient presents with hepatitic pattern of LFT derangement, initial approaches include advice about losing weight, cutting alcohol intake, and stopping all possible medications.

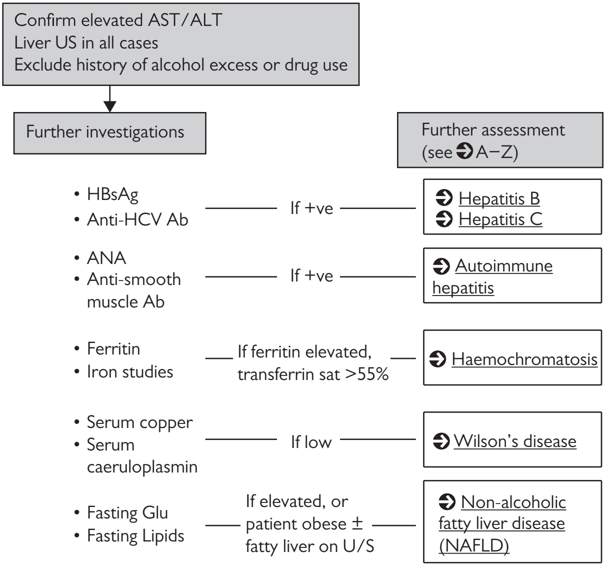

Confirm elevated AST/ALT
Liver US in all cases
Exclude history of alcohol excess or drug use
Further investigations
Further assessment (see ➔ A–Z)
• HBsAg
• Anti-HCV Ab
If +ve
➔ Hepatitis B
➔ Hepatitis C
• ANA
• Anti-smooth muscle Ab
If +ve
➔ Autoimmune hepatitis
• Ferritin
• Iron studies
If ferritin elevated, transferrin sat >55%
➔ Haemochromatosis
• Serum copper
• Serum caeruloplasmin
If low
➔ Wilson's disease
• Fasting Glu
• Fasting Lipids
If elevated, or patient obese ± fatty liver on U/S
➔ Non-alcoholic fatty liver disease (NAFLD)

Fig. 1.10 Approach to investigation of raised transaminases.

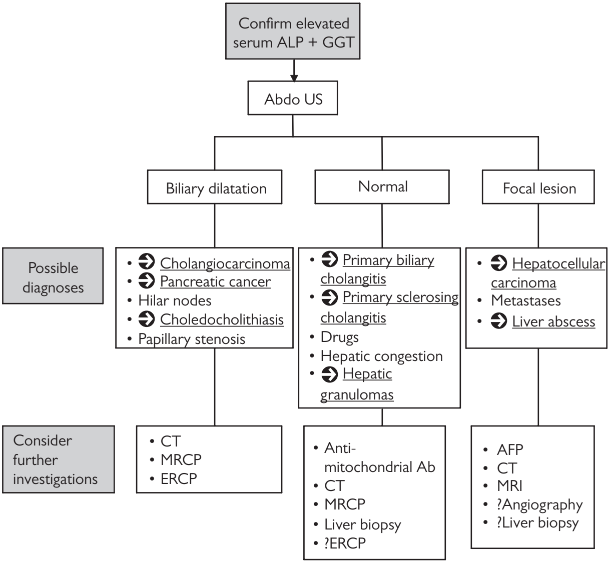

Confirm elevated serum ALP + GGT
Abdo US
Biliary dilatation
Normal
Focal lesion
Possible diagnoses
• Cholangiocarcinoma
• Pancreatic cancer
• Hilar nodes
• Choledocholithiasis
• Papillary stenosis
• Primary biliary cholangitis
• Primary sclerosing cholangitis
• Drugs
• Hepatic congestion
• Hepatic granulomas
• Hepatocellular carcinoma
• Metastases
• Liver abscess
Consider further investigations
• CT
• MRCP
• ERCP
• Anti-mitochondrial Ab
• CT
• MRCP
• Liver biopsy
• ?ERCP
• AFP
• CT
• MRI
• ?Angiography
• ?Liver biopsy

Fig. 1.11 Approach to investigation of raised cholestatic LFTs.

Section 2

Clinical practice and diagnostics

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Patient issues

Gastrointestinal examination

Overview

Clinical examination narrows the differential diagnosis and focuses investigation. GI examination is an extension of the general examination, as diseases in most systems can cause signs in the GI tract (e.g. right heart failure causing hepatomegaly and ascites). Full examination is rarely possible in a busy clinic but may be tailored to a particular anatomical area or disease spectrum (see Boxes 2.1 and 2.2); however, a systematic approach should be used for all patients.

Initial inspection

First impressions count! Explain you wish to examine the patient, and try to put them at ease. It is particularly difficult to elicit abdominal signs in tense patients. Does the patient look well or sick? Are they thin and malnourished? (e.g. prominent cheek bones, obviously loose-fitting clothes) (see ▶ Approaches to unintentional weight loss). Note any skin changes: jaundice, pigmentation (➔ haemochromatosis), excoriations (biliary obstruction), and rashes (➔ erythema nodosum, ➔ pyoderma gangrenosum, ➔ dermatitis herpetiformis).

Hands

Start with the hands. A handshake may be the first physical contact, which patients find less intrusive than heading straight for the abdomen. Check temperature (cold hands in GI haemorrhage may signify significant blood loss), pulse rate and volume, and blood pressure. Lying and standing BPs *essential* in GI bleeding to assess postural drop (see ▲ **acute upper gastrointestinal bleeding** ▲).

Examine nails: may be white (leukonychia, marker of low albumin), spoon-shaped (koilonychia, marker of iron-deficiency anaemia), or clubbed (associated with chronic liver disease, ➔ inflammatory bowel disease, suppurative GI inflammation).

In patients with liver disease, look for asterixis (indicates ▲ **hepatic encephalopathy** ▲). This is *not* a resting tremor, but transient ↓ in muscle tone. Ask patient to 'stop the traffic' (arms extended at elbows, wrists, and fingers). Look for coarse jerky flap at the wrist and fingers.

Controversy. What is the mechanism of clubbing?

An often quoted theory is that vasodilatation or reactive thrombocytosis enhances release of growth factors, resulting in soft tissue expansion. This theory is many years old, and unproven.

Box 2.1 Extraintestinal features of chronic liver disease

- Hands: clubbing, palmar erythema, Dupuytren's contracture.
- Spider naevi: >5 pathological.
- Gynaecomastia in ♂, with associated loss of axillary hair.
- Testicular atrophy.

Box 2.2 Extraintestinal features of inflammatory bowel disease

- Hands: clubbing.
- Joints: arthropathy (especially large joints), sacroiliitis.
- Skin: erythema nodosum, pyoderma gangrenosum.
- Eyes: keratoconjunctivitis, scleritis, uveitis.
- Perianal: skin tags, fistulae, abscess.

Head, neck, and precordium

- **Eyes** Look for conjunctival pallor (anaemia), jaundice, episcleritis/uveitis (➔ inflammatory bowel disease). Yellow deposits around eyes (xanthelasma) suggest hypercholesterolaemia, potentially related to ➔ primary biliary cholangitis. Kayser–Fleischer rings occur in ➔ Wilson's disease.
- **Face** Absence of malar fat pads suggests malnutrition/cancer cachexia. 'Moon face' results from excess steroid exposure (iatrogenic or Cushing's syndrome). Pseudo-Cushing's and parotid enlargement seen in ➔ alcohol use disorder.
- **Mouth** Look for oral ulceration (➔ inflammatory bowel disease, ➔ coeliac disease, ➔ Behçet's disease), angular stomatitis (seen rarely with iron or vitamin deficiency), and oropharyngeal candidiasis (possible immunocompromise). Brown macules on lips suggest ➔ Peutz–Jegher syndrome, and telangiectasia on lips and tongue ➔ hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu syndrome; see Plate 3) or systemic sclerosis. Poor dentition and gum hypertrophy may be linked with malnutrition or alcohol excess.
- **Neck** With patient at 45°, examine for raised jugular venous pressure as a guide to intravascular filling and right heart function. Palpate from behind for cervical and supraclavicular lymphadenopathy (?Virchow's node in ➔ gastric cancer). With patient sitting forward, check for nephrectomy scars (a classic exam 'catch out'!).
- **Precordium** Examine for spider naevi (central arteriole feeding multiple draining capillaries, >5 pathological) and, in ♂, loss of axillary hair and palpable breast tissue (gynaecomastia), suggestive of chronic liver disease.

Abdomen

The patient should be lying flat, with the abdomen fully exposed, and arms by sides.

Inspection

- Look for scars from previous surgery. Distension may be related to ascites, bowel obstruction, masses, pregnancy, or obesity. Striae indicate rapid ↑ in abdominal girth.
- Bruising around flanks (Grey Turner's sign, from retroperitoneal bleeding) or umbilicus (Cullen's sign, from intraperitoneal bleeding) associated with severe ➔ acute pancreatitis.
- Dilated superficial abdominal veins running longitudinally should be checked for direction of flow. Put forefingers of both hands together on the vein, then separate along it by 6cm maintaining compression, then remove inferior fingers. Veins will all rapidly refill if there is underlying inferior vena cava obstruction but only those above umbilicus will refill if the cause is portal hypertension. Very rarely, veins radiate out from the umbilicus (caput medusa) because of ➔ portal hypertension and portosystemic shunting in the presence of a patent umbilical vein.

Palpation

- **Light palpation** Ask about areas of tenderness. Start furthest away from painful sites if present, or in LIF. Lightly palpate all 4 quadrants: guarding or rebound tenderness suggest peritonism.
- **Deep palpation** of abdomen, separate from viscera, is important and should include both iliac fossae, epigastrium, and periumbilical areas. Sigmoid colon easy to feel in slim people; ascending and descending colon retroperitoneal and not normally felt. Differential diagnosis for masses shown in Fig. 2.1.
- **Liver** Palpate gradually from RIF towards right subcostal margin in 3cm steps, with patient taking slow deep breaths. Hepatomegaly (Box 2.3) usually felt at least 2cm below right costal margin, although prominent Reidel's lobe may lead to this being incorrectly diagnosed. Although hepatomegaly may be feature of all chronic liver diseases, advanced cirrhosis classically causes volume loss. Note texture of the lower border: irregular and firm suggests ➔ cirrhosis or ➔ hepatocellular carcinoma; smooth and tender may indicate acute ➔ hepatitis.

  It is logical to percuss immediately after palpation. A depressed diaphragm, such as in COPD, may push liver down, giving impression of hepatomegaly. Always percuss upper border of liver (a 12cm span in the mid-clavicular line is upper limit of normal).
- **Spleen** Deep palpation again begins in RIF, advancing towards left subcostal margin in stepwise movements. Splenomegaly (Box 2.4) usually requires doubling in size before palpable. May be differentiated from enlarged left kidney as you cannot 'get above it', it moves towards RIF with respiration, a 'notch' may be palpable, it is not ballotable, and percussion should be dull over splenic bed (9th intercostal space, mid-axillary line).
- **Kidneys** One hand is placed in left or right hypochondrium, and the other in corresponding flank. The hand under the patient is pressed firmly upwards towards the other. A large kidney may be 'ballotable'.

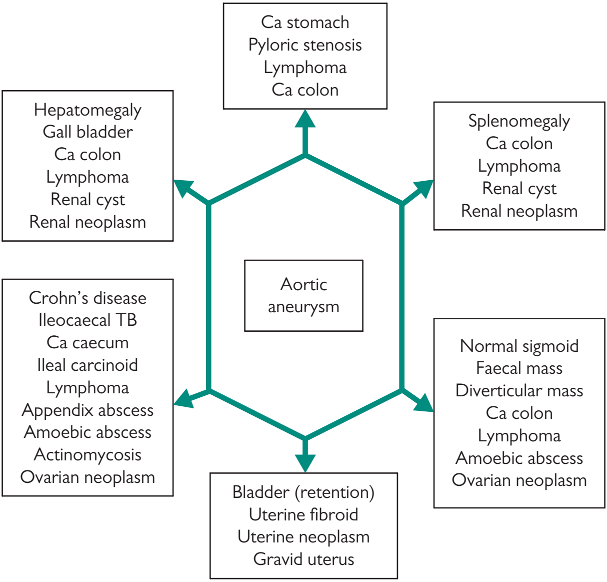
Ca stomach
Pyloric stenosis
Lymphoma
Ca colon
Hepatomegaly
Gall bladder
Ca colon
Lymphoma
Renal cyst
Renal neoplasm
Splenomegaly
Ca colon
Lymphoma
Renal cyst
Renal neoplasm
Aortic aneurysm
Crohn's disease
Ileocaecal TB
Ca caecum
Ileal carcinoid
Lymphoma
Appendix abscess
Amoebic abscess
Actinomycosis
Ovarian neoplasm
Normal sigmoid
Faecal mass
Diverticular mass
Ca colon
Lymphoma
Amoebic abscess
Ovarian neoplasm
Bladder (retention)
Uterine fibroid
Uterine neoplasm
Gravid uterus

Fig. 2.1 Differential diagnosis of abdominal masses. AAA, abdominal aortic aneurysm; Ca, carcinoma.

Box 2.3 Causes of hepatomegaly

- **Acute inflammation**: viral hepatitis, alcoholic hepatitis, drug-induced hepatitis (e.g. paracetamol overdose)
- **Venous congestion**: right ventricular failure, tricuspid regurgitation, constrictive pericarditis, Budd–Chiari syndrome
- **Mass lesions**: cystic disease, liver abscess (pyogenic, hydatid or amoebic), neoplasia (benign or malignant)
- **Infections**: malaria, leptospirosis, actinomycosis
- **Chronic liver disease**: all causes (see Approach to cirrhosis and chronic liver disease)
- **Granulomatous hepatitis**: see Hepatic granulomas
- **Metabolic diseases**: non-alcoholic fatty liver disease, Gaucher's disease, histiocytosis X, amyloidosis, glycogen storage diseases
- **Blood disorders**: sickle cell anaemia (sequestration), thalassaemia major (extramedullary haematopoiesis), myeloproliferative disorders

Box 2.4 Causes of splenomegaly

- ➔ Portal hypertension*
- Haemoglobinopathies: ➔ sickle cell anaemia (in children, prior to autoinfarction), thalassaemia major*, autoimmune haemolytic anaemias
- Infection: EBV*, malaria, leishmaniasis, ➔ schistosomiasis*, subacute bacterial endocarditis, brucella, histoplasmosis
- Myeloproliferative disorders: myelofibrosis*, chronic myeloid leukaemia*, lymphoma, polycythaemia rubra vera, ➔ systemic mastocytosis
- Metabolic diseases: storage diseases (e.g. Gaucher's disease*), ➔ amyloidosis*
- Other: tropical splenomegaly syndrome, ➔ sarcoidosis, ➔ SLE, ➔ Felty's syndrome

*May cause hepatosplenomegaly.

Percussion

To elicit **ascites**, initially percuss left flank. If clearly resonant, no need to examine further. If dull, percuss back towards midline, where it should become resonant. Ask patient to roll towards you, into right lateral position. Wait 30s, then percuss back towards left flank, looking for 'shifting dullness'. While the patient is in this position, palpation again under left costal margin may allow splenomegaly to be detected (much more effective than trying to 'lift up' spleen with left hand placed under posterior ribs, as sometimes advocated).

Auscultation

Listen for bowel sounds to identify signs of obstruction ('tinkling') or ➔ ileus (absent). Occasionally renal artery bruits or hepatic bruit (related to ➔ hepatocellular carcinoma) may be identified.

Completing the examination

Examine hernial orifices, and consider whether rectal examination is indicated (Box 2.5). ❗ In young ♂ with acute central abdominal pain, examine genitalia so as not to miss testicular torsion.

Box 2.5 Digital rectal examination (DRE)

'If you don't put your finger in it, you put your foot in it'

(Old English medical saying, unattributed)

Traditionalists may argue that DRE is as central to proper general examination as measuring BP. But just as tumour markers are a poor screening test in the absence of a clinical indication, yield from 'speculative' PR is very low, and it is found unpleasant by many patients. Nevertheless, DRE should not be avoided due to embarrassment (on behalf of the doctor or the patient) or where there is the possibility of pathology (e.g. unexplained weight loss, anaemia). A chaperone should be offered. To perform correctly:

- Patient lying on the left side ('left lateral').
- Press posteriorly on anal skin with pulp of gloved lubricated index finger of right hand (allows relaxation of anal tone and easy passage of finger).
- Do not simply stick in finger at right angles to anus—this causes reflex contraction of the anus and surprise (if not pain) to patient.
- Look for perianal pathology (see Box 2.2).

> 'It is easier to find men who will volunteer to die, than to find those who are willing to endure pain with patience' (Julius Caesar)

Pain control

- Pain associated with GI disease may be due to a range of mechanisms, including inflammation (e.g. ➲ inflammatory bowel disease, peritonism), hollow viscus obstruction (e.g. ➲ biliary colic), tumour invasion (e.g. ➲ pancreatic cancer), or abnormal GI motility or pain sensation (e.g. ➲ irritable bowel syndrome). See also ▲ **acute abdominal pain** ▲ and ▶ Approach to chronic or recurrent abdominal pain.
- Pain control is often suboptimal (and potentially dangerous), without a clear diagnosis of its cause. That said, absence of a diagnosis should not defer treatment of acute pain. Opioids do not mask clinical signs of peritonism.
- WHO recommend a three-step 'pain ladder':
  - **Step 1:** Prompt oral administration of non-opioids (e.g. paracetamol 1g qds, or NSAIDs such as ibuprofen 400mg tds). Consider adjuvant use (e.g. amitriptyline 10–25mg for neuropathic pain).
  - **Step 2:** Mild opioids (e.g. codeine 30–60mg PO qds, dihydrocodeine 30mg PO qds, tramadol 50–100mg PO qds) ± non-opioids ± adjuvants. Note that codeine is very dependent on conversion to morphine by CYP450 2D6 for analgesic activity; up to 10% of population are poor metabolizers, so if ineffective consider switch to alternative weak opioid before escalating.
  - **Step 3:** Strong opioids (morphine 5–10mg 4 hourly PO/SC/IM/IV; use half the dose if administering parenterally) ± non-opioids ± adjuvants. Note when converting that 60mg codeine is equivalent to 6mg morphine, and 100mg tramadol is equivalent to 10mg morphine. Slow-release preparations, including fentanyl 25–100μg transdermal patch every 72h, useful for chronic pain but not in acute setting.

- Stepwise increase in opioids advised until patient pain free. Normal-release opioids (morphine sulfate solution or tablets) given 'by the clock' (4 hourly), rather than 'on demand'. Same dose used for 'breakthrough' pain, as frequently as 1–2 hourly. Total daily intake used to calculate 4-hourly requirement for next day. Once satisfactory maintenance achieved, swap to 12 or 24 hourly slow-release preparations. Oxycodone preferred for patients with renal failure.
- Prevent opioid-induced constipation using stool softener and stimulant laxatives (e.g. co-danthramer 25/200 in 5ml od PO AND senna 2 tabs at night PO, or sodium docusate 200mg bd PO). → ANTI-EMETICS may be needed (cyclizine 50mg tds PO/IM/IV, → METOCLOPRAMIDE 10mg tds PO/IM/IV), particularly for 1st week.
- Involve the experts (e.g. palliative care service, pain team).
- The type of GI disease will influence the approach to pain control:
  - **Functional bowel disorders** (e.g. ➔ irritable bowel syndrome, simple constipation) may benefit from behavioural therapies (➔ biofeedback, cognitive therapy, hypnotherapy). Antispasmodics may relieve colicky pain (e.g. mebeverine 135–270mg PO tds).
  - **Pancreatic disease** Opioids often required for cancer and ➔ chronic pancreatitis. Percutaneous/EUS-guided coeliac plexus block (with bupivacaine + triamcinolone) useful, but usually short term. Radiotherapy may reduce ➔ pancreatic cancer pain.
  - **Decompensated liver disease** NSAIDs may worsen liver and renal dysfunction, and risk GI bleeding. Opioids may cause ▲ **hepatic encephalopathy** ▲, particularly if precipitate constipation. Paracetamol is the safest analgesic, but at a dose of ≤3g/d. If opioids are required, morphine or fentanyl are preferred, but at ↓ dose and frequency (e.g. qds), and with careful monitoring.

End-of-life care

Recognizing when someone is nearing the end of their life is notoriously difficult and not an exact science. Signs may include ↑ drowsiness, confusion, or restlessness; visions of people and places that are not present; involuntary movements; ↓ socialization and withdrawal; ↓ need for food and fluids, with loss of appetite; ↓ urine output; cooling of peripheries; and rattling sounds while breathing, with irregular shallow respiration. Historically end-of-life care has often been less than satisfactory, yet the health professional has a huge opportunity to help ensure a good death for the patient and a salutary experience of this for the relatives.

General approach

- Are there any potentially reversible causes for deterioration that would be reasonable in the circumstances of the individual patient to investigate and treat? May include: dehydration/acute kidney injury, infection, drug toxicity, steroid or alcohol withdrawal, or metabolic disturbance (↑/↓ Na^+, ↑ Ca^{2+}, ↑/↓ glucose).
- Discuss prognosis and agree goals, and preferred place of care with the patient if possible, or welfare attorney, and with any family or friends that patient would (to best of your knowledge) want involved in their care. Take account of any advance care planning or documented patient wishes.

- Agree, document, and communicate individual care plan, including decision about cardiopulmonary resuscitation. Explain that all care and treatments of benefit will continue and be regularly reviewed.
- Patients should be supported to continue to take food and drinks as long as they are able to do so and want to. Artificially providing nutrition and hydration to patients who are rapidly deteriorating is unlikely to delay death and may cause significant discomfort (for example, overhydration can contribute to distressing respiratory secretions). Where indicated, slow SC fluid infusions may be considered.
- Ensure the patient has an appropriate pressure mattress to minimize skin breakdown, and that they are regularly repositioned for comfort. Patients should receive regular eye, mouth, bladder, and bowel care.
- Consider and regularly review appropriateness of ongoing monitoring of vital signs and blood sugar, as well as of any investigations. Document clearly which interventions are not appropriate.
- Review and stop any medications not consistent with agreed goals of care. For those that continue, ensure routes prescribed are appropriate. If the patient is able to swallow, oral medications can continue, but if this is becoming difficult consider switching to liquid or subcutaneous formulations.
- Make sure anticipatory medications for common symptoms available and prescribed for as required use (see next).
- If patient or family needs are complex, contact palliative care team for support and advice.
- Identify whether there are any emotional, cultural, family, legal, religious, or spiritual issues that need to be addressed to provide holistic care. Identify whether any family members are at increased risk of severe bereavement reactions and seek additional support. Sensitively explore wishes regarding organ donation, if relevant.
- Ensure comprehensive handover to other team members, who may include out-of-hours on-call staff, the patient's GP, and community services. Record plan of how and when to contact family if the patient deteriorates or dies.

Prescribing

All patients should have as required medication for symptom control for:

- Pain. See ⊳ pain control. If patients not on regular opioids, initiate morphine or diamorphine 2.5mg SC prn. Consider need for co-prescription of laxatives if this will improve patient comfort. Opioids should not be used for the sole purpose of sedation.
- Nausea/vomiting. See → ANTI-EMETICS.
- Agitation. Midazolam 2–5mg, hourly prn (also useful as anticonvulsant). If converted to SC infusion, usually titrated in 5–10mg steps. If insufficient, can add in haloperidol 2mg SC od/bd, but be aware can ↑ QT on ECG.
- Breathlessness. Oxygen only improves breathlessness if patient hypoxic. Nasal prongs often better tolerated than masks. Fans can help relieve symptoms, as can more upright position. Midazolam 2–5mg SC hourly, or (dia)morphine 2.5mg SC 2 hourly, can relieve symptoms if these measures not sufficient.

- Respiratory tract secretions. Reduce risk by avoiding fluid overload, and changing patient position. Intermittent SC injections often work well, for example, hyoscine butylbromide SC 20mg hourly.
- If a symptom becomes established and regular medications required, calculate 24h prn requirements and convert to syringe driver, alongside ongoing prn prescriptions for breakthrough symptoms. Review at least daily.

Breaking bad news

Effective, empathetic communication is the cornerstone of good medicine. The skill and care with which bad news is broken often defines all further interactions between doctors and their patients/relatives, for good or ill. The need to break bad news may cover a wide range of scenarios, including a new diagnosis of cancer, a cancelled procedure, or complications from an intervention. In the UK, there is a statutory duty of candour, whereby healthcare organizations have a duty to inform patients as soon as possible of any unintended or unexpected incident in their care that, in reasonable opinion of healthcare professional, could result in or appear to result in death (not relating to natural progression of an illness) or severe or moderate harm (including psychological harm). An explanation is required as to what is known at time, what further enquiries will be made, an apology offered, and a written record of notification must be kept. Patients should be given reasonable support, and must receive written notes of the initial discussion and notification.

Although the specific approach needed will depend on the individual situation, a number of considerations apply to most cases:

- Give thought beforehand as to what you will say. It is vital you are as informed as possible about the patient's specific case.
- Try to see the patient and/or their relatives in quiet environment, free from interruptions. Breaking bad news in a private room is always preferable to open ward or waiting room. Turn off mobile phones/bleeps.
- Ensure the patient's nurse is with you, so they can provide further support and are aware of what has been said.
- Explain things as simply as possible. Avoid jargon. Draw simple diagrams where appropriate.
- Be honest. If a mistake or complication has occurred, evasion and dishonesty always compound an already difficult situation. If you have informed the patient of an event where something has gone wrong and caused (or has potential to cause) harm or distress, document that the disclosure has been made in accordance with statutory duty of candour.
- Record your discussions in the notes and ensure the patient's GP is aware of any important new developments. Little is more unsatisfactory for a GP than to see a patient in community to discuss their new diagnosis of cancer, about which GP knows nothing.
- Try to be encouraging and reassuring, but not falsely optimistic. For example, while finding malignancy may be a shock to patient, confirming the diagnosis often allows specific treatment to be planned.
- Avoid overspeculation or hypothesis.

- Don't worry about expressing emotion. Maintaining professionalism does not mean displaying a cold, dispassionate approach. In times of grief or upset, patients and relatives appreciate that their doctor understands and empathizes with their distress.
- Don't rush. There are always time pressures, but providing the space for questions to be asked in an unhurried way is important.
- Don't delegate responsibility downwards. If you feel uncomfortable breaking bad news, ask your senior to do it, and accompany them. You may learn vital lessons on how to (and maybe how not to!) approach this vital area of practice. Similarly, if issue relates to a complication or medical accident, be sure to discuss situation with your consultant, who may wish to see patient/relatives themselves.
- One response to bad news may be anger. Acknowledge this, but never respond in kind.
- Don't leave things 'in the air'. Whether the bad news relates to a serious diagnosis, cancelled admission, or complication, patients wish to know what next step entails. Provide information about other sources of support (e.g. patient liaison service or national support groups).
- Relatives occasionally state that their loved one 'wouldn't want to know' if they had cancer, terminal disease, etc. This may present a difficult situation, requiring sensitive handling. It has been shown that patients generally want more, not less, information. Sometimes a lack of acceptance by relatives underlies the aforementioned statement. While it is important to keep the family 'on board', the primary duty is to the patient, who has a right to know what is going on with his/her body. Scenarios in which relatives, but not the patient, are aware of a serious diagnosis often develop in a messy and wholly unsatisfactory manner for all involved.
- Finally, accept this is a stressful and often difficult situation. If your approach is to be honest, thoughtful, and compassionate, you won't go far wrong. Take time to reflect on how the conversation went, and have a low threshold to discuss the situation and your feelings about it with a supportive colleague.

Complaints

Almost every clinician at some point in the career will have to respond to a complaint. Most will be simply dealt with and often resolved immediately face-to-face, but some will be more complex and require investigation and negotiation (see also discussion on duty of candour in ➢ breaking bad news, p. 138). Common themes of complaints are:

- Communication.
- Treatment outcomes.
- Appointments, hospital admissions, and discharge arrangements.
- Consent.
- Support and supervision of junior staff.

An awareness of events and issues that are high risk for triggering complaints may allow potential problems to be avoided.

Complaints that escalate are not necessarily those in which clinical care was unreasonable, but rather where a reasonable person could not be expected to understand the explanation provided. Quality of local handling and feedback to patients is key. All hospitals will have their own complaints procedure, and if a patient or relative wishes to complain, they can be made aware of the local Patient Advice and Liaison Service (PALS) or complaints manager. These can coordinate a local resolution service. If this fails, complainants can seek independent review, which may include the Health Service Ombudsman.

Receiving a complaint is unsettling, particularly if you feel you took extra care with that patient. It is not unusual to feel upset, shocked, or even betrayed. When responding to a complaint:

- Try not to panic or take the complaint personally (more easily said than done).
- Your complaints manager will help you, and should be the person to coordinate the hospital's response. There is normally a deadline: if you are going on leave, or may have any other difficulty meeting this, tell the manager as soon as possible.
- Seek advice from your consultant (if you are a trainee) and/or your defence organization. This is not breaching patient confidentiality.
- You should be given access to the relevant clinical case notes, even if you have since changed employer. Review these in detail. Hospitals may also have a standard template for responses.
- Respond openly, apologize if this is what is needed, and ensure you act on the outcome of any investigation. If you are in the wrong, see this as a point for learning and improvement.
- Answer only what applies to you, but address all concerns raised (no matter how trivial they might seem). Try to see things from complainant's perspective.
- Stick to facts, although it may be acceptable to state how you felt at the time of an event (for example, if you thought the complainant's behaviour was intimidating and this had a material impact on care).
- It is possible that you could be being blamed for system problems, or what is in fact reasonable practice. If you were following directions from a more senior colleague or specialist, say so, and who this person was. If you were guided by a specific protocol, state which one and what version.
- If you do not remember something you are claimed to have said or done, state that you have no recollection of this. If complainant's version of events is different from yours, describe what happened from your perspective. There may be genuine misunderstandings or words misheard.
- Be aware that what you write could be visible to the complainant, particularly if the court system becomes involved. Do not make facetious remarks. If you are typing a response, make sure any tracked changes are accepted and only the finalized draft is authorized. Ask the complaints manager to let you see the response that is to be sent to the complainant.
- If the complaint is predominantly directed at one of your colleagues, offer constructive support to help them through what can be a difficult process.

Medically unexplained symptoms

Sometimes patients present with persistent symptoms for which thorough examination and focused investigation does not identify explanatory pathology. These may account for up to 20% of GP consultations, and are common in GI practice (particularly non-cardiac chest pain, globus, dyspepsia, bloating, abdominal cramps, and perceived altered bowel habit). Risk factors include anxiety and depressive disorders, childhood adversity or abuse, ♀ gender, and severe illness or death of a close relative. There can be concerns on both sides about serious diagnoses being missed, which can drive extensive, unproductive, and occasionally harmful investigations. While often frustrating to patient and physician alike, clinicians can make a difference to patient well-being even when symptoms remain unexplained.

- Take the patient seriously and let them know that you believe them. Identify their worries and expectations, and show your interest.
- Ask open questions and let patients tell the story fully in their own way. Go right back to the beginning. Focus on the impact of symptoms. Acknowledge and validate the patient's sense of suffering.
- Watch for signs that you are not hearing the patient. This can manifest as repetition, or new or amplifying symptoms.
- Summarize back to patient what you think you have heard. Be open about your uncertainty and willingness to check your understanding. Where possible, use patient's own language and expressions to offer tangible explanations of what is causing the symptoms. Be clear on what is not wrong, and why.
- Do not use 'medically unexplained symptoms' as a diagnosis. Focus instead on the symptom and its consequences, rather than the name.
- Physicians often approach such cases by minimizing and treating empirically, whereas often patients are really searching for explanations and emotional support. Doctors may assume patients want more than they do, and precipitate premature tests and referrals through pressure to diagnose and cure. Indicate how common such symptoms are and concentrate on helping patients manage these and improve function. Sometimes more senior clinicians may feel safer managing this complex patient group than their junior colleagues, and it is important to keep open a clear path for consult or support.
- The doctor–patient relationship can be therapeutic in its own right. Be reassuring, keep an open mind, and be willing to reassess if things change. Be explicit about your thoughts and feelings. Manage expectation. Proactively communicate with other clinicians.
- Fatigue is extremely common, and underexplored. Recognize and acknowledge its impact. Exercise can help.
- Depression is up to 4× more common in patients with medically unexplained symptoms (either as cause or consequence), and addressing low mood helps with symptom control.
- Safety net. Reassure patients that they will always be taken seriously, with a willingness to reassess. Bear in mind that 4–10% do go on eventually to have organic explanation for their presentation.
- Discuss and document about 'red flag' symptoms and signs, and agree actions (and in what timescale) if the situation changes.
- Discuss alternatives for support rather than hospital-based care.

Use of evidence

Treatment decisions should be based on reliable data. All clinicians must be able to critically appraise scientific literature to determine what to translate into their practice. It is important to read systematically through relevant papers, rather than just relying on brief initial abstracts. Points to consider include:

- Study question. Was it well-defined pre-hoc and clinically relevant?
- Patients. Who was included in, and excluded from, the study? Do the characteristics of these patients align with those who you would consider using the proposed new treatment for in your practice (i.e. are the data generalizable)?
- Intervention. What intervention was delivered, and is this applicable to how it would be performed in your practice (again, are results generalizable)?
- Control group. Was there a control group, and if so was this against best available therapy or placebo? While use of placebo arms can be helpful in early development as ↓ required sample sizes, it provides little robust information as to whether you should replace current standard of care. Were patients in both trial arms otherwise treated in same way? Ideally interventional studies should use a sham procedural control—while there has been much debate about the ethics of subjecting patients to such procedures, there is now extensive literature demonstrating how wrong conclusions have been reached by not incorporating such a control arm.
- Outcomes. Was the primary outcome pre-specified and clinically meaningful? Be wary of outcomes with a subjective element (e.g. imaging, endoscopy, or histology images)—it is prudent to include more than one blinded reader for such endpoints. Also be wary of surrogate endpoints, where measures are used with presumption that they predict true relevant clinical outcome (e.g. liver function tests (LFTs) as a predictor of liver transplant). Often these relationships are imperfect, and there are numerous examples where wrong conclusions have been drawn.
- Allocation. Was allocation randomized to eliminate selection bias, and how was this performed? Could there have in fact been any predictable allocation?
- Blinding. Ideally trial should be performed double-blind, where neither investigator nor patient knows which treatment was received. Be vigilant for any way blind could be inadvertently broken, for example infusion reactions only occurring with active drug.
- Was a power calculation performed pre-hoc to estimate sample size to reliably measure a clinically meaningful difference (post-hoc power calculations are of almost no value)? Were adequate numbers of patients then recruited? Was the trial designed to demonstrate superiority, equivalence, or non-inferiority of the new intervention?
- Follow-up. How long were patients followed-up for (gives an indication as to durability of treatment benefit).
- Drop-out and missing data. Was drop-out the same between both groups, and how were subjects who dropped out (or other missing data) accounted for? Reasons why this might be uneven could include patients developing more adverse effects from active drug, or receiving no benefit from placebo, and these need to be reflected in final analysis to minimize bias from these factors. Can be achieved using intention-to-treat analysis.

- How are data reported? Trials often present results in terms of relative risks and odds ratios, which can look like dramatic differences. However, most clinicians and patients find it easier to understand absolute risk reduction (ARR). For example, a 50% relative reduction may look impressive, but if outcome in question occurred in only 2% of the control group, this means it occurred in 1% of the treatment group. This is an ARR of only 1% (far less impressive!). Another concept helpful here is number needed to treat (NNT), defined as 1/ARR. Here, a 1% ARR gives a NNT of 100—that is, you would have to treat 100 patients with the new treatment to have confidence that 1 of them would experience benefit.
- Post-hoc analyses. Can be informative and hypothesis generating, but remember the trial design is typically only fully informative about the primary outcome. If no benefit was seen here, be wary of overinterpreting possible benefits in secondary outcomes or subgroup analyses. Multiple comparisons in data sets should be regarded with scepticism, as it is possible to 'find' statistical significance by chance alone when enough analyses are performed. If this approach has been used, has there been correction applied to account for multiple comparisons?

Patient-centred outcomes

While traditionally physicians have focused on survival and physiological metrics to determine treatment success, there has been a progressive move to incorporate outcomes of care rated as important by patients. There is likely to be an increasing focus on measures such as absenteeism and presenteeism from work, and years lived with disability, to deliver value-based healthcare. Key concepts to understand with any measure include:

- Reliability. Precision and reproducibility of the score.
- Validity. How well the score truly measures the important variable.

Important to recognize that scores can have ceiling effects: they often measure burden of disease but not degree of 'wellness', can be insensitive in patients with mild or low physiological burden disease, and the degree of change that is meaningful or clinically relevant is often controversial.

Quality-of-life scores

Understanding patient health-related quality of life (HRQL) scores is important in both clinical management of chronic disease (particularly disorders that lack measurable physical indices of disease severity, such as ➔ irritable bowel syndrome) and interpreting the research literature. Numerous instruments available. Some are generic global health scores; others are digestive disease specific.[1] Useful scores include:

- Gastro-oesophageal reflux disease: GORD-HRQL[2]
- Hepatitis/chronic liver disease: HQLQ[3]
- ➔ Inflammatory bowel disease: IBDQ[4]
- ➔ Irritable bowel syndrome: IBS-QOL.[5]

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[1] Yacavone RF *et al.* (2001). *Am J Gasteroenterol* **96**: 285–97.

[2] Velanovich V *et al.* (1996). *J Am Coll Surg* **183**: 217–24.

[3] Bayliss ML *et al.* (1998). *Qual Life Res* **8**: 39–55.

[4] Guyatt G *et al.* (1989). *Gastroenterology* **96**: 804–10.

[5] Patrick DL (1998). *Dig Dis Sci* **43**: 400–11.

Patient-reported outcomes (PROs)

These are health outcomes directly reported by patient who experienced them, rather than through (and possible with interpretation by) an intermediary, such as a physician or nurse. Increasingly used to understand treatment efficacy in both trials and clinical practice, and many are available in electronic form (ePROs). As with HRQL scores, may be generic or disease specific.[6,7,8]

Patient panels

Patient panels are set up to provide input and perspective into how healthcare services are designed and delivered, and guide which outcomes are most relevant in clinical practice and research, to the intended recipients' needs. They act as a forum through which patients can advise and advocate to improve patient experience, help improve communication between service provider and users, share decision-making, and in some cases there may be a legal obligation for healthcare provider to consult with a panel.

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[6] Hindryckx P *et al.* (2018). *Gut* **67**: 61–9.

[7] Khanna P *et al.* (2014). *Am J Gastroenterol* **109**: 234–48.

[8] de Jong MJ *et al.* (2018). *Clin Gastroenterol Hepatol* **16**: 648–63.

Blood tests and special investigations

Blood tests

Haematology (see also ► Approach to anaemia)

- Be aware of lower limits of normal Hb (120g/L for ♀, 130g/L for ♂). Normal ranges: 145 ± 25 g/L and 155 ± 2.5 g/L, respectively.
- Microcytosis and macrocytosis provide valuable clues to aetiology, but be cautious when interpreting MCV as dimorphic blood film can give average value within normal limits (although red cell distribution width (RDW) will be raised).
- An abnormal platelet count can be informative (see Table 2.1).

Table 2.1 Causes of low and high platelet counts

High platelet count	Inflammation, bleeding, essential thrombocythaemia
Low platelet count	Liver disease, ITP, drugs, ↑ consumption (HUS, TTP, DIC)

Haematinics (see also ➲ iron, ➲ vitamin B_{12}, ➲ folic acid)

- Best tests for diagnosing iron deficiency are iron-binding saturation (more or less the same as transferrin saturation) and low ferritin (note: high ferritin can be difficult to relate to total iron stores as it is an acute phase protein; if CRP ↑, ferritin needs to be >100 to exclude iron deficiency). TIBC helpful in differentiating iron-deficiency anaemia (↑) from anaemia of chronic disease (normal or ↓), although the two can coexist.
- B_{12}. Check antiparietal cell and anti-intrinsic factor antibodies if ↓ vitamin B_{12} to exclude ➲ pernicious anaemia. If negative, investigate for dietary deficiency, other causes of distal small bowel malabsorption, and terminal ileal disease.
- Folic acid can be measured in serum (most straightforward, and sufficient in most cases) or in red cells (provides better estimate of long-term status).

Liver function tests (LFTs)

Conventional 'liver function' tests (AST, ALT, ALP, γGT) provide little information about synthetic function of liver. This is best indicated by serum albumin, clotting (prothrombin time), and bilirubin.

Bilirubin (normal serum range 3–17μmol/L)

Increased levels may reflect ↑ production (e.g. haemolysis), ↓ hepatic uptake/conjugation (e.g. ➲ Gilbert's syndrome), ↓ hepatocyte function, or ↓ biliary excretion (e.g. ➲ choledocholithiasis). See ► Approach to recent-onset jaundice.

Prothrombin time (PT; normal range ~12–15s, but lab-specific)

In absence of vitamin K deficiency (excluded by giving vitamin K 10mg PO/IV/d for 3d), PT provides good indicator of liver synthetic function. Strong prognostic indicator of poor outcome and need for ➔ liver transplantation in ▲ **acute liver failure** ▲ and after ➔ paracetamol overdose ∴ do not correct PT in this setting (e.g. with fresh frozen plasma) unless bleeding.

Albumin (normal serum range 35–50g/L)

Reasonable indicator of liver synthetic function. In chronic liver disease, reflects disease severity and prognosis (see ➔ Child–Pugh score). Always consider other causes of low albumin: malnutrition, severe intercurrent illness (↓ as acute phase reactant), renal losses (nephrotic syndrome), and gut losses (➔ protein-losing enteropathy).

Aspartate aminotransferase (AST; normal range 5–45IU/L)

Intracellular enzyme present in number of tissues other than hepatocytes (erythrocytes, cardiac and skeletal muscle, kidney, brain). As with ALT, ↑ levels in many types of liver disease, but >1,000IU/L suggests acute hepatocyte injury due to drugs (e.g. ➔ paracetamol overdose), viruses (e.g. ➔ hepatitis A, B, C or E), or ischaemia (e.g. hypotensive episode, cardiac embolic source: AF, endocarditis). AST >2x ALT characteristic of ➔ alcoholic liver disease.

Alanine aminotransferase (ALT; normal range 5–50IU/L)

Also intracellular enzyme, but more specific than AST for hepatocyte injury. ALT>AST often found in viral hepatitis and ➔ non-alcoholic fatty liver disease.

Alkaline phosphatase (ALP; normal range 40–165IU/L)

Present in biliary epithelial cells, bone, intestine, and placenta. Isoenzyme may identify source, but associated ↑ γGT rarely makes measuring this necessary. ↑ ALP seen in intrahepatic cholestasis (e.g. ➔ primary biliary cholangitis) or extrahepatic biliary obstruction (e.g. ➔ pancreatic cancer).

Gamma-glutamyl transpeptidase (γGT; normal range 10–60IU/L)

Marker of cholestasis, but may ↑ due to alcohol and other enzyme inducing drugs. Extensive investigation of ↑ GGT, in absence of other LFT derangement, rarely identifies significant pathology.

Amylase

- In ➔ acute pancreatitis, serum amylase ↑ 6–12h after onset. Levels >1,000U/L strongly indicative of diagnosis in correct clinical setting. Diagnosis should not rely solely on amylase, which may not be significantly ↑ because of underlying ➔ pancreatic insufficiency (with acinar cell loss ∴ unable to make amylase), or if pancreatitis due to hypertriglyceridaemia (as biophysical limitation to measuring in serum, but can still detect ↑ amylase in urine). Amylase concentration does not predict prognosis. Serum lipase sensitive and specific, and ↑ levels persist for longer, but assay less readily available.
- **Non-specific serum elevation** Usually <1,000U/L, seen in:
  - Wide range of abdominal causes (including ➔ appendicitis, ➔ cholecystitis, ➔ choledocholithiasis, perforation, and salpingitis.
  - Diabetic ketoacidosis.
  - Salivary gland source in mumps or parotitis.

  - Macroamylasaemia. Chronic elevation. No clinical relevance and can be differentiated from pancreatic amylase by absence of amylase in urine.
  - ↓ Excretion in renal impairment.
- **In other fluids**. High levels in ➲ pancreatic pseudocysts help differentiate from ➲ pancreatic cystic tumours. Raised levels in ascites diagnostic of pancreatic ascites due to pseudocyst or pancreatic duct rupture. High levels in pleural effusion in pancreaticopleural fistula.

Organ-specific special investigations

Gut hormone profile

- Measurement of serum gut hormones (Table 2.2) can be an invaluable part of investigation of patients with suspected ➲ neuroendocrine/pancreatic endocrine tumours. However, completely invalid results may be obtained if sample are not taken or handled correctly.
- Serum chromogranin A correlates quite well with tumour burden in well-differentiated neuroendocrine tumours, but may also be ↑ in prostatic cancer. Levels can also vary with certain foods.

Patient preparation

→ H_2 RECEPTOR ANTAGONISTS should be stopped for 72h, and → PROTON PUMP INHIBITORS for 3wk, before blood taken. After an overnight fast, take blood (10ml).

Table 2.2 Gut hormone profile

Hormone	Normal range	Disease association
Chromogranin A	0–38ng/L	➲ Carcinoid
Gastrin	0–40pmol/L	➲ Gastrinoma
Vasoactive intestinal polypeptide (VIP)	0–30pmol/L	➲ VIPoma
Somatostatin	0–150pmol/L	Somatostatinoma
Pancreatic polypeptide (PP)	0–300pmol/L	Role in appetite regulation: ↓ levels associated with Prader–Willi syndrome

Sample preparation

- Inform laboratory you are taking sample and when, and of patient's serum calcium and urea, all drugs currently administered, clinical question, and details of any gastric surgery (see also ➲ gastrinoma).
- Transfer 10ml of blood into heparin tube (containing aprotinin 0.2ml, 2,000kIU). Mix by inversion. Place on ice and transfer immediately to laboratory. Plasma should be separated in refrigerated centrifuge and frozen at –20°C within 15min of venepuncture for subsequent analysis.

Tumour markers

Alpha-fetoprotein (αFP)

Normally produced by liver and foetal yolk sac. Causes of ↑αFP:

- ➲ Hepatocellular carcinoma (HCC). Levels ↑ in 70–80%, and >1,000ng/ml in 40% of patients.
- Non-seminomatous germline tumours.
- Some GI tumours (➲ gastric, biliary tract, ➲ pancreatic cancer).
- Active liver disease (cirrhosis, viral hepatitis).
- Ataxia-telangiectasia.
- Pregnancy with babies with neural tube defects or Down syndrome.

Although level of αFP may correlate with size of HCC, it is not ↑ in 30%, and ∴ not of use alone as screening or surveillance test. May also be ↑ in 5% of patients with chronic liver disease (particularly during flare, as indicated by ↑ ALT/AST). However, αFP >100ng/ml always necessitates excluding HCC by US, contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI).

Carbohydrate antigen 19-9 (CA19-9)

Tumour marker primarily of value in monitoring treatment response and/or progression of ➲ pancreatic cancer. Little value as screening tool, as also ↑ in other GI cancers (particularly ➲ colonic cancer), pancreatitis, hepatic cirrhosis, and biliary obstruction. Can get false-negative in patients who lack Lewis antigen on RBCs (~1% of Caucasian population), as CA19-9 not expressed.

Carcinoembryonic antigen (CEA)

Glycoprotein discovered in 1965 in association with ➲ colonic cancer, and embryonic and foetal gut tissues. CEA has low diagnostic ability to detect primary colon cancer, as ↑ in various malignant diseases (breast, lung, ➲ gastric and ➲ pancreatic cancers), as well as non-malignant conditions (➲ gastritis, ➲ peptic ulcer disease, liver disease, heavy cigarette smoking, chronic bronchitis, and pancreatitis). Measuring CEA not useful as a screening test, even when applied to patients with GI signs or symptoms. Also poor measure of tumour bulk because it is highest when liver involved, even to only minor degree, and may be barely ↑ in patients with bulky intra-abdominal recurrence. With these caveats, there are some defined roles for CEA (Box 2.6).

Box 2.6 Rules for measuring CEA

- Prognostic indicator: Preoperative CEA level related to stage of ➲ colonic cancer. May predict surgical incurability. Values >5ng/ml imply poorer prognosis, independent of surgical stage.
- Persistent disease: Postoperative CEA level may serve as measure of completeness of tumour resection. If preoperatively elevated CEA value does not fall to normal within 4wk (a period twice plasma half-life of CEA) after surgery, resection probably incomplete or occult metastases present.
- Recurrence: CEA level may help monitor for tumour recurrence.
- CEA assay may also serve as monitor of treatment response in metastatic disease. Serial values parallel tumour regression or progression. Rising CEA is incompatible with tumour regression, whereas values ↓ in most patients who have responded to treatment.

Therapeutic drug monitoring (TDM) in IBD

See also ➔ Crohn's disease and ➔ ulcerative colitis.

TDM available for several IBD therapies. Incorporating can explain and sometimes mitigate lack of efficacy, loss of response, and much of drug toxicity.

Thiopurines

- → THIOPURINES (azathioprine/mercaptopurine) have been a mainstay of IBD treatment for >30y. However, associated with adverse effects in up to 40%.
- Therapeutic effect and toxicity mediated by intracellular metabolites, with efficacy related to thioguanine nucleotide (TGN) concentrations, and hepatotoxicity to methylmercaptopurine (MMP).
- Once absorbed, azathioprine is non-enzymatically converted to mercaptopurine. Can then be metabolized through 3 enzymatic pathways: to thiouric acid (by xanthine oxidase, inhibited by allopurinol), MMP (by thiopurine methyltransferase; TPMT) and TGN.
- *TPMT* gene is highly polymorphic: 0.3% of population have homozygous mutations with absent or very low activity, 9% have heterozygous mutations with intermediate activity, and 90% have normal or high activity. Patients with low or intermediate activity are at risk of myelosuppression due to excess accumulation of TGN (explains 25% of thiopurine myelosuppression).
- TPMT heterozygotes with low or intermediate activity should have initial dose ↓ by 30–70%. Homozygotes with absent or very low activity should avoid thiopurines altogether. Patients with very high activity may need ↑ doses, guided by clinical response, TGN and MMP levels.
- TGN levels correlate with therapeutic response, and levels between 235–450pmol/8×10^8 RBCs ↑ likelihood of remission 5-fold. Levels exceeding this range associated with myelotoxicity.
- In up to 20% of patients failing therapy, thiopurine metabolism is skewed towards excessive MMP production. These patients can be identified by low TGN in presence of high MMP, particularly if ratio exceeds 24, and further dose escalation frequently results in disproportionate escalation of MMP and hepatotoxicity. Combining a lower (25%) dose of thiopurine with allopurinol often leads to efficacy without excess toxicity.
- A therapeutic strategy is shown in Table 2.3.

Table 2.3 Therapeutic drug monitoring to guide dose adjustment with lack of thiopurine efficacy

TGN	MMP	MMP/TGN ratio	Cause of drug failure	Strategy
↓	↓	Normal	Inadequate dose	Increase dose
↓	↑	↑	Excess TPMT activity	Reduce dose of thiopurine by 75% and add in allopurinol
↓	↓	Normal	Lack of compliance	Confirm compliance
Normal	Normal	Normal	True drug ineffectiveness	Alternative therapy

Biologics

- Assays available for measurement of serum levels of → ANTI-TNF DRUGS (particularly infliximab and adalimumab), and corresponding anti-drug antibodies, although performance varies between different laboratories. Multiple studies have confirmed correlation between clinical and endoscopic response and trough levels of anti-TNF medications. Infliximab trough levels of 3–7μg/ml and adalimumab trough levels of at least 7.5 mic/ml are suggested for maintenance therapy in UC and Crohn's disease.
- Assays for → VEDOLIZUMAB are available. Levels above 20 μg/ml at week 6 of therapy appear to be associated with improved clinical outcomes.
- Anti-drug antibodies explain a substantial proportion of secondary loss of response (if neutralizing) and hypersensitivity.
- In patients with persistent disease activity despite treatment with a biologic, drug levels can be measured to confirm adequate exposure.
  - If levels adequate, consider adding in immunomodulator, switching to drug with alternative mechanism of action, or surgery.
  - If levels low, check for anti-drug antibodies. If present, switch to another drug in same class (e.g. infliximab to adalimumab) or to another therapeutic class. If these are low/absent, verify patient concordance with drug, and if confirmed intensify dose if safety allows.

Schilling test

Historically used in ➲ vitamin B_{12} deficiency to identify cause. Now very rarely (if ever) performed. Reagents discontinued around 2003.

Stool tests

Faecal calprotectin

Faecal marker, extremely sensitive to gut inflammation (as principally derived from neutrophils). Can help ↓ need for endoscopy and guide response to treatment and aetiology of symptoms (inflammatory vs. functional) in ➲ Crohn's disease and ➲ ulcerative colitis, but only in context of remainder of clinical picture and investigations. ❗ However, do not use (in isolation) to diagnose new onset rectal bleeding/bloody diarrhoea, as screening/surveillance tool for polyps/CRC, or in patients >40y or with new change in bowel habit. See BSG Guideline 2016. 🖱 https://www.bsg.org.uk/resource/bsg-guidance-on-the-use-of-faecal-calprotectin-testing-in-ibd.html.

Faecal elastase

See ⊳ 'Pancreatic function tests', p. 153.

Stool microscopy

Historically very useful test to establish inflammatory cause of diarrhoea. Invasive pathogens such as *Shigella* and *Campylobacter* lead to many polymorphs and red blood cells, whereas toxigenic organisms and viruses produce watery stool containing few formed elements. Acute exacerbations of ulcerative colitis also produce WBCs and RBCs in stool, giving appearances that resemble bacillary dysentery. However, test now largely superseded by ⊳ faecal calprotectin.

Faecal occult blood tests (FOBTs)

- Qualitative tests that rely on oxidation of colourless compound to coloured one in presence of pseudo-peroxidase activity of haemoglobin and developer solution of hydrogen peroxidase in alcohol. Cheap, readily available, convenient, but distasteful for patients to carry out. Relatively high false-positive and negative rate (Box 2.7). Most tests positive when blood loss >2ml/d. Positive predictive value ~20% for adenomas and 5–10% for cancers.
- Newer tests ↓ false-positive rates while maintaining sensitivity. In UK, ➤ colorectal cancer screening and surveillance until recently used guaiac-based test, but now being replaced by faecal immunochemical test (FIT), which has greater sensitivity and specificity.

Breath tests

Wide variety of volatile compounds in expired air relate to aspects of digestive function. For urea breath tests, see ➲ *Helicobacter*.

Box 2.7 Limitation of faecal occult blood test (FOBT)

False-positive tests

- Exogenous peroxidase (e.g. vegetable peroxidase in broccoli, turnips, cauliflower, radishes, melon).
- Non-human haemoglobin: red meat.
- Other GI bleeding (epistaxis, gingival bleeding, haemorrhoids).
- Aspirin and NSAIDs, which ↑ upper GI bleeds.

Recommendation: avoid red meat, peroxidase-containing vegetables, vitamin C, and NSAIDs for 3d before and during testing. Avoiding iron preparations also recommended, although evidence is weak.

False-negative tests

- Haemoglobin degradation by storage or faecal bacteria.
- Ascorbic acid (vitamin C) interferes with indicator dye.
- Lesion not bleeding at time of sampling.

Recommendation: develop slides within 4–6d. Do not rehydrate slides for average risk screening. Two samples from each of three consecutive stools should be tested.

Hydrogen breath tests

Sole source of hydrogen in mammals is bacterial fermentation. Increased breath hydrogen easily detected using hand-held meter and does not involve radioactive substrates. Rise from baseline >20ppm after oral ingestion of 50g lactose identifies ➲ lactose intolerance.

An early rise in breath hydrogen is seen within 2h of glucose or lactulose ingestion in patients with small intestinal ➲ bacterial overgrowth (all people show late rise due to colonic fermentation); conventional testing uses ↑ of 20ppm, which has good specificity but poor sensitivity, especially if low doses (<20g) of test carbohydrate used. Sensitivity improved by ensuring that dinner preceding overnight fast contains readily absorbed carbohydrates to avoid high basal level on day of test, measuring increase at 6h rather than 4h, and having cut-off of 10ppm over baseline for diagnosing malabsorption.

With ↑ awareness of roles of fructans in ➔ irritable bowel syndrome and use of low FODMAP diet, fructose breath test increasingly used to identify fructose intolerance.

Despite these precautions and attractions of ease of performance and avoidance of radioactive tracer, many authorities regard hydrogen breath tests as insufficiently sensitive or specific. Recent consensus document has been published.[9]

Carbon breath tests

- ^{14}C-triolein breath test measures $^{14}CO_2$ after ingestion of labelled triglyceride. Test utility insufficient to justify equipment expense and radiation exposure ∴ not widely used.
- The sugar xylose is catabolized by aerobic Gram-negative overgrowth flora; following 1g oral dose of [^{14}C]-D-xylose, ↑ $^{14}CO_2$ found in 85% of people with small bowel bacterial overgrowth.
- Urea breath tests use urea labelled with ^{13}C or ^{14}C for identification of ➔ *Helicobacter pylori*.

Pancreatic function tests

- Malabsorption and steatorrhoea only occur when >90% exocrine pancreas function lost. Exocrine function tests used to assess ➔ chronic pancreatitis and other causes of exocrine ➔ pancreatic insufficiency.
- **Direct tests** involve sampling pancreatic secretions after administration of secretagogue (e.g. secretin, cholecystokinin). Duodenal aspirates measured for volume, bicarbonate, and enzyme concentration (e.g. amylase, trypsin, lipase). Direct tests remain 'gold standard', but invasive to perform and rarely used in clinical practice.
- **Indirect tests** measure consequence of exocrine insufficiency. Cheaper and easier to perform ∴ more commonly used.
  - **Faecal elastase 1 (FE1)** commonly used as simple, non-invasive, and accurate (sensitivity/specificity >90% for significant exocrine insufficiency). Levels <200μg/g stool may indicate exocrine insufficiency, but can be falsely low in watery diarrhoea. Level <50μg/g stool highly specific. Measurement not affected by concomitant use of → PANCREATIC SUPPLEMENTS.
  - **3d faecal fat** Normally <7% of ingested fat appears in stool, but steatorrhoea only develops if pancreatic lipase output falls to <10% of normal, so test is poorly sensitive for mild to moderate pancreatic insufficiency. Unpleasant for patients and laboratory staff, and rarely performed in modern practice.

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[9] Rezaie A *et al.* (2017). *Am J Gastroenterol* **12**: 775–84.

GI physiology/motility testing

Oesophagus

Oesophageal manometry and assessment of motility

Commonly used techniques to investigate ➔ oesophageal motility disorders include:

- Intraluminal manometry.
- Radiological studies using barium swallows or video fluoroscopy.

Radionuclide imaging to quantify bolus transit through the oesophagus is largely a research tool and not further described. Standard endoscopy is a poor method for assessing oesophageal function, although there is some interest in using small-calibre endoscopes transorally or transnasally to diagnose tracheobronchial aspiration and test sensory thresholds.

Manometry

Gold standard for assessing oesophageal body motility as a quantitative approach. Equipment includes transnasally passed catheters with multiple water-perfused small-calibre lumens or more high-tech solid state devices using pressure transducers embedded into probe at various levels. Developments in telemetry allow temporary fixation of pressure transducers at the level of the lower oesophageal sphincter and recording of data on a belt device (e.g. BRAVO procedure).

Reading a manometry report

Four aspects of function need to be characterized to enable most disorders to be diagnosed:

- Peristaltic performance: percentage of swallows with progressive contraction sequences.
- Contraction wave configuration (amplitude and duration).
- Lower oesophageal sphincter basal and peak pressures.
- Lower oesophageal sphincter relaxation with swallowing.

Limitations of manometry

- Poor toleration of probe by some patients.
- Longitudinal muscle contraction can result in axial displacement.
- Cannot distinguish muscular from neurological problems.

Guideline

BSG guideline on manometry and oesophageal reflux monitoring, 2019. 🖱 https://www.bsg.org.uk/wp-content/uploads/2019/11/Oesophageal-manometry-and-oesophageal-reflux-monitoring.pdf.

Radiological assessment (barium swallow with videofluoroscopy)

Essential to study oropharyngeal phase of swallowing and upper oesophageal sphincter, and offers less invasive alternative to manometry in some patients. Can be used by speech therapists working with radiologists to develop compensatory strategies to minimize tracheobronchial aspiration in patients with oropharyngeal swallowing disorders. Limitations include subjective evaluation, study of only small number of swallows, lack of standardization of details of swallowing technique (such as bolus size), and time delays between swallows.

Oesophageal pH monitoring

Ambulatory 24h pH monitoring is the most widely used test to investigate gastro-oesophageal reflux and correlate symptoms with reflux. Involves positioning transnasal pH probe 5cm above lower oesophageal sphincter (determined manometrically). Patient then conducts life as normally as possible while recording symptoms, meals, and sleep in diary. Oesophageal acid exposure is defined as pH <4; this should occur for <3.5% of total recording time (arbitrary threshold; there is no value that reliably identifies GORD patients).

Not necessary in most patients with typical reflux symptoms but can be useful in patients with refractory or atypical symptoms not responding to empirical treatment.

Recent technology allows measurement of alkaline reflux from duodenum into oesophagus using different probe positioned in exactly same way. Can allow rational prescribing with prokinetics such as → DOMPERIDONE or mucosal protective agents such as → SUCRALFATE in patients with symptomatic reflux not responding to empirical acid suppressant treatment.

Oesophageal impedance monitoring

Intraluminal impedance monitoring can be used to detect flow of liquids and gas through hollow viscera. Works by detecting changes in resistance to current flow when bolus traverses electrode pair, and can distinguish liquid (low impedance) from gas (high impedance) boluses. Electrode pairs placed at multiple sites on a standard solid state oesophageal manometry catheter can track antegrade bolus transit through oesophagus to correlate with manometry findings. In contrast, electrode pairs placed at multiple sites on standard pH probe can track retrograde bolus transit from stomach to oesophagus to correlate with pH. In combination with manometry, used for oesophageal function testing and while manometry provides information on contractile activity, impedance provides information on bolus transit. Especially helpful in patients with non-obstructive dysphagia, but less suitable for evaluation of achalasia. Usage in combination with pH monitoring makes gastro-oesophageal reflux monitoring more complete as allows recognition of both acidic and weakly acidic reflux episodes. Results of several studies suggest impedance—pH monitoring is useful in evaluating patients with PPI-resistant typical reflux symptoms, chronic unexplained cough, excessive belching, and rumination.

Stomach

Gastric emptying and measurement of gastric motility

Major function of the stomach is to act as food reservoir and control delivery to intestine. Delayed emptying produces post-prandial fullness, bloating, nausea, and vomiting. Causes outlined in Box 2.8.

Diagnosis

Mechanical obstruction best excluded with endoscopy or barium studies. Non-invasive scintigraphic techniques are the main clinical tools for assessing gastric motor function; different isotopes can be used to study emptying of solids and liquids. Reports of abnormal electrical rhythms studied with electrogastrography (EGG) and found to be associated with abnormal gastric emptying and its symptoms have recently appeared. Clinical application requires further clarification.

Box 2.8 Causes of delayed gastric emptying

Mechanical obstruction

- ➔ Pyloric stenosis:
  - Adult hypertrophic pyloric stenosis.
  - Chronic benign ➔ peptic ulceration.
  - ➔ Gastric cancer.
- ➔ Bezoars.
- Duodenal tumour.
- Pancreatic disease (e.g. ➔ pancreatic cancer, ➔ chronic pancreatitis).

Impaired motility

- Autonomic neuropathy:
  - ➔ Diabetes.
  - Shy–Drager syndrome.
  - ➔ Parkinson's disease.
- Infiltrative, e.g. ➔ amyloidosis.
- Collagen vascular disease, e.g. ➔ systemic sclerosis.
- Post-surgical:
  - Vagotomy.
  - ➤ Roux-en-Y anastomosis.
- Drugs:
  - Anticholinergics.
  - Opiates.
  - Tricyclic antidepressants.
- Other:
  - Post-viral (e.g. CMV).
  - Trauma (e.g. head injury).
  - ➔ Dermatomyositis.
  - Pregnancy.
  - Myotonic muscular dystrophy.
  - Hypothyroidism.
  - ➔ Anorexia nervosa.

Liver and pancreas

Sphincter of Oddi manometry

Manometric assessment of biliary and pancreatic sphincters can be used in assessment of pancreaticobiliary type pain (see ➔ sphincter of Oddi dysfunction). However, use becoming less frequent due to variable correlation of manometry findings with outcome after endoscopic therapy and high rates of post-ERCP pancreatitis.

Hepatobiliary scintigraphy (e.g. HIDA scan)

Hepatobiliary iminodiacetic acid (HIDA) scan employs radioactive tracer that is excreted by liver into bile. Sequential scanning over 2h then performed. Delayed tracer clearance may suggest impaired bile drainage. Indications include suspected cholecystitis (including assessment of cystic duct patency), investigation of biliary-type pain, suspected bile leaks, and ➔ sphincter of Oddi dysfunction. In practice, HIDA scanning has largely been replaced by other imaging modalities.

Lower GI tract

Colonic transit studies

Defined as delayed transit of radio-opaque markers through proximal colon (see Box 2.9). Classically found in ~70% of patients (most often young to middle-aged ♀) consulting for infrequent defaecation non-responsive to therapeutic intervention (see → LAXATIVES, and ➲ biofeedback). Unlike patients with normal colonic transit, show no signs of psychological distress and may have physiological basis to symptoms. Although resting motility appears normal, there seems to be failure to ↑ motility after meals, suggesting abnormality of enteric plexus. Patients with severe colonic inertia may also have ↓ oesophageal motility, delayed transit through small intestine, and high incidence of bladder dysfunction.

Box 2.9 Colonic transit studies

Technique used to study patients with severe constipation and otherwise normal GI investigations. Patients take high fibre diet and avoid laxatives, enemas, or any medications that may affect bowel function. Results can only be interpreted if procedure strictly adhered to.

- Day 1, 09.00. Patient takes 1 capsule (containing 20 radio-opaque markers) in water.
- Day 5, 09.00. Supine AXR. If no markers seen, discontinue study (as no evidence of slow transit).
- Day 7, 09.00 Supine AXR. Slow-transit constipation diagnosed if >80% of markers retained.

Anorectal manometry

Important technique in evaluating problems with defaecation. Perfused probes or pressure-sensitive transducers are introduced into the rectum to record anal sphincter pressures, sensitivity to rectal distension, and presence of rectoanal inhibitory reflex.

Clinical assessment of anal sphincter tone by digital examination very inaccurate, so manometry indicated in patients complaining of constipation (see ▶ Approach to constipation) or ➲ faecal incontinence where clinical assessment of sphincter function important. Resting anal pressures and maximal voluntary squeeze pressures can be measured. If high resting pressure, normal reflex relaxation response to rectal distension is assessed—this is absent in ➲ Hirschsprung's disease. High threshold for initiation of reflex anal relaxation may indicate problem with rectal compliance (e.g. Hirschsprung's megarectum) or afferent sensory pathways (e.g. spinal cord injuries). Defects in voluntary squeeze suggest abnormal innervation of external sphincter. Normal voluntary squeeze but low resting pressure suggest problem in internal sphincter, which can occur after haemorrhoid surgery or in conditions such as diabetes and systemic sclerosis. In constipated patients with normal resting pressure and normal rectoanal inhibitory reflex, anatomical abnormalities such as accentuated puborectalis angulation or internal ➲ rectal prolapse should be considered.

Defaecography studies

Method of evaluating defaecation in patients who complain of excessive straining, or who employ digital manipulation to facilitate evacuation. Traditionally done with barium thickened to consistency that approximates stool; introduced into rectum, and its evacuation is monitored fluoroscopically. ➔ MRI defaecography (see below) has almost entirely replaced barium studies. Allows assessment of anorectal anatomy, and measurement of anorectal angle (angle between axis of rectum and that of anal canal: usually ~90°) at rest and during defaecation. Rectocoeles and intussusceptions not seen at rest may be seen during evacuation. Degree of perineal descent can also be assessed, which gives information on integrity of puborectalis and other pelvic floor muscles.

Imaging

Plain radiography

- Advances in other imaging modalities have significantly ↓ the role of plain radiography, but it still continues to have its uses.
- Films are often taken with patients supine, but erect and lateral decubitus views provide better delineation of gas patterns in abdomen.

Indications and findings

- **Viscus perforation** Air under diaphragm on erect CXR suggests perforation (but may be non-pathological finding post-laparoscopy or following percutaneous endoscopic gastrostomy insertion). Retroperitoneal perforation may be suggested by air around kidneys or a clearly defined psoas muscle margin.
- **Bowel obstruction** Large gastric air bubble may suggest gastric outflow obstruction. Small bowel obstruction appears as dilated (>35mm) central bowel loops (erect films only), with valvulae conniventes traversing bowel. Colonic dilatation suggested by transverse colon >60mm or caecum >90mm, and air–fluid levels within small bowel loops.
- **Aerobilia** Air delineating biliary tree suggests previous sphincterotomy, biliary surgery, or stone passage. Usually reflects adequate biliary drainage.
- **Colitis** Appearances may include featureless colon with ↓ haustral patterns, 'thumb-printing' (due to haustral thickening and wall oedema), and toxic colonic dilatation. Constipation often occurs proximal to colitis, and so stool within colon in active colitis may give hint of disease extent.
- **Calcified lesions** Renal stones radio-opaque in 90%, gallstones in 10%. Calcification may occur due to chronic pancreatitis, long-standing cysts, granulomas (e.g. s to TB), lymph nodes, blood vessels, benign tumours, and (rarely) in malignant tumours.

Contraindications

- Balancing risks of radiation exposure vital (e.g. usually completely contraindicated in pregnancy, especially 1st trimester). One AXR ≡ 35 CXRs.

Barium contrast studies

Contrast studies of the GI tract can be performed using single or double-contrast techniques. Barium is agent of choice unless worries about bowel viability or perforation, in which case avoided because free barium in peritoneal cavity causes inflammatory reaction. Water-soluble contrast such as ➔ Gastrografin® can be used instead. Single contrast uses low density barium to look for filling defects or contour abnormalities. Double contrast uses smaller amounts of high contrast barium with gas, giving much better resolution of fine mucosal detail.

Barium swallow and contrast examination of upper GI tract

Traditionally, barium swallow was initial investigation for dysphagia, but most clinicians now use endoscopy as 1st choice. However, video fluoroscopy with water-soluble contrast is preferred method of assessing swallowing dysfunction. Contrast studies can be useful in demonstrating sliding ➲ hiatus hernia or gastro-oesophageal reflux, and in giving information about strictures that may be impassable endoscopically (e.g. in oesophagus or duodenum).

Small bowel studies

Traditional techniques of small bowel meal and small bowel ⊳ enteroclysis historically used frequently in evaluating variety of small bowel diseases including tumours, inflammatory pathology such as ➲ Crohn's disease, and ➲ Meckel's diverticulum. Contrast studies can be useful in diagnosing level of small bowel obstruction, although water-soluble contrast should be used in this situation. Diagnostic yield in obscure GI bleeding poor. These studies are now largely superseded by ⊳ video capsule endoscopy, ⊳ small bowel MRI, and small bowel US.

Barium studies of colon

Technique becoming much less common because of availability of colonoscopy and development of CT colonography. Contraindications include toxic megacolon, ischaemic colitis, or other diseases where bowel wall friable and more likely to perforate.

Ultrasound

- Widely available imaging modality with useful and unique property of enabling imaging blood flow and soft tissues in real time. Results depend on user expertise, particularly for specialist work. In particular, transabdominal US may provide useful information concerning intestinal disease (e.g. wall thickness) in expert hands. Endoscopic ultrasound (EUS) (see ⊳ p. 212) with guided needle tissue sampling functions has greatly advanced diagnosis of lesions within or accessible from the intestinal lumen (Box 2.10).
- Technique works by emitting high frequency (1–20MHz) sound waves from transducer. These reflect back to differing degrees, dependent on underlying tissue, and are converted into electric pulses and sent back to analyser which provides images of tissues and distance from skin. Higher frequency waves produce more detailed images, but penetrate less deeply into body (2–5MHz generally used for abdominal US, and 7.5–12MHz for EUS). Doppler sonography allows real-time information on blood flow within a morphological image.
- Most useful information provided when a specific question is asked (e.g. 'Is there biliary tree dilatation?' rather than 'abdo US').

Box 2.10 Strengths and weaknesses of transabdominal US

Strengths

- Ability to display flow and soft tissue in real time.
- Spatial resolution superior to CT and MRI.
- Safe and well tolerated: no ionizing radiation.
- Can be performed at the bedside (i.e. portable).

Weaknesses

- Technically challenging.
- Not good in obese or gaseous patients.
- Inability to see beyond gas/bone–soft tissue interface.
- Relatively poor contrast resolution, improved with media for contrast-enhanced US.
- Findings less reliable the farther area of interest is from skin probe (e.g. retroperitoneal structures, pancreas).

Indications

Hepatobiliary

- US 1st line modality for most diffuse and focal hepatobiliary abnormalities. Ideal for cystic lesions, and >90% sensitive and specific at identifying stones in gallbladder (but only 50% sensitive when stones in common bile duct). Can also detect splenomegaly.
- Most advocate ➢ liver biopsy to be done under US control (alternative is CT).
- Doppler allows flow in large blood vessels (e.g. see ➲ portal vein thrombosis, ➲ Budd–Chiari syndrome, hepatic artery patency in liver transplant recipients), and even vascularity of large lesions to be assessed.

Pancreatic

- In ➲ acute pancreatitis, US can detect gallstones and biliary dilatation, although CT is more sensitive in evaluating pancreatic disease overall.

Luminal GI tract

- Useful for evaluating RLQ pain and possible appendicitis (although CT often used in acute setting), especially in young ♀ when it can be helpful in distinguishing appendiceal from ovarian pathology. US may help diagnose terminal ileal inflammation or stricturing (e.g. due to ➲ Crohn's disease), diverticulitis, small bowel obstruction, and bulky mesenteric nodes or GI neoplasms.
- Excellent for diagnosing intraperitoneal fluid collections such as ascites, abscesses, or haemorrhage, and also guiding percutaneous needle aspiration for definitive diagnosis.

CT scanning

Collimated X-rays through patient produce a series of attenuation profiles that are computed into cross-sectional images (usually 3–8mm cuts depending on machine/clinical indication). Continuous motion (helical or spiral CT) has replaced sequential acquisition. Tissue contrast achieved as tissues attenuate X-rays to differing degrees. Whole abdomen can be scanned within 1 breath-hold. Adiposity improves definition (in contrast to ➢ ultrasound). Sequentially timed imaging after injection of iodine-based IV contrast produces characteristic appearances of lesions/disease in arterial, venous, or portal venous phases. Specific acquisition protocols depend on clinical question.

Indications for CT in GI disease are wide-ranging and include investigation of ▲ **acute abdominal pain** ▲, cancer diagnosis and staging (e.g. ➲ pancreatic and ➲ oesophageal cancer); assessment of pancreatic, biliary, and liver disease; and investigation of intra-abdominal collections. Targeted biopsy of lesions may be performed by CT or US, depending on anatomical site and local expertise.

Few **contraindications**, but include renal failure (IV contrast can damage kidneys further), pregnancy, and iodine allergy. Discuss with radiologists whether useful information may be gained from unenhanced CT.

CT pneumocolon ('virtual colonoscopy')

Technique of imaging colon following insufflation using helical CT scanning. Colon usually cleansed using same ➢ bowel preparation as conventional colonoscopy. Images reconstructed to give 'virtual colonoscopy' that can include views behind folds that may be difficult with conventional colonoscopy. Wide variation in results of clinical trials investigating CT as screening tool for ➲ colon cancer, but some report similar sensitivity of virtual and conventional colonoscopy in detecting colon polyps >6mm in diameter.

Intestinal contents can also be 'tagged' with orally ingested contrast; subtracting tagged material at the image processing stage provides a further diagnostic test ('faecal tagging CT'), which avoids need for bowel preparation while providing ~80% sensitivity and specificity (Box 2.11).

Box 2.11 CT scanning and radiation risk

- Average UK background radiation exposure = 2.3mSv/y.
- Estimated risks from diagnostic medical imaging based primarily on extrapolation from exposed populations at much higher doses, including atomic bomb survivors (exposed to >50mSv), cancer radiotherapy, and occupational exposures (>40mSv).
- Excess malignancy not clearly demonstrated by epidemiological studies below 100mSv. However, a 'linear, no threshold' model is assumed. Lowest dose with some evidence of i risk is 20mSv.
- Radiation exposure for abdominal CT 10mSv (equivalent to 500 CXRs). PET/CT exposure= 25mSv. Therefore, any more than 2 scans falls within potential deleterious range, with estimated risk of cancer death = 1 in 2,000.
- Although individual risk small, this is applied to large population, particularly with adoption of colorectal cancer screening.
- Alternatives to CT should be considered in young (who are more susceptible), and those likely to need repeated imaging.
- Avoid in pregnancy if at all possible, especially 1st trimester.

Enteroclysis

Radiological technique of examining small intestine that involves intubation of duodenum or proximal jejunum, usually combined with metoclopramide to accelerate small bowel transit. Provides better luminal distension than oral ingestion of contrast. However, intubation not pleasant for patient, and technique requires extra time and expertise from radiologist. Now rarely used due to alternative techniques for imaging small bowel (see: ▷ video capsule endoscopy, ▷ small bowel MRI, and small bowel ▷ luminal US.

Magnetic resonance imaging (MRI)

Patient is placed within a strong magnet, which causes hydrogen nuclei (protons) to align with the magnetic field. A radiofrequency pulse displaces the protons, and on switching off the pulse the protons relax back to alignment and release absorbed radiofrequency energy, which is detected. 'T1 and T2 weighted' refer to relaxation constants related to timing of proton realignment. Different tissues display different T1/T2-weighted characteristics. MRI does not use radiation.

Indications for MRI in GI disease include staging of ➲ pancreatic cancer and defining other solid lesions (usually as 2nd line to ▷ CT), and investigation of small bowel or fistulating perianal disease (see ➲ Crohn's disease). MR cholangiopancreatopathy (MRCP) used in delineation of biliary and pancreatic ductal anatomy, allowing higher-risk ▷ ERCP to be reserved for therapy.

Contraindications include claustrophobia, morbid obesity (e.g. >60cm abdominal diameter), displaceable metal in situ (e.g. cochlear implants, although note that modern cardiac pacemakers are MRI safe, and majority of older models do not preclude MRI if scanning protocols adapted). MRI is a more expensive and longer procedure than CT.

Magnetic resonance cholangiopancreatography (MRCP)

MRCP allows detailed imaging of the biliary and pancreatic ductal systems, without risk of invasive procedure such as ERCP. MRCP 92% sensitive and 97% specific for detection of bile duct stones, although stones <3mm may be missed and air bubbles may be mistaken for stones in biliary tree. Scanning before, and minutes after, secretin injection enhances pancreatic ductal imaging in suspected ➲ chronic pancreatitis and ➲ sphincter of Oddi dysfunction. Important modality for assessing biliary strictures.

Small bowel MRI

MRI's properties of good soft tissue contrast, multiplanar imaging, and avoidance of ionizing radiation make it attractive for small bowel imaging. Speed and effective oral contrast agents give MRI role in differentiating small bowel from adenopathy (frequent cause of confusion on CT), differentiating masses outside small bowel, and defining intrinsic small bowel pathology including neoplasms, IBD, and fistulae.

MR proctography (MR defaecography, 'dynamic pelvic MRI')

Used for assessing pelvic floor abnormalities. Can be performed in a closed- or open-configuration MR system, allows dynamic evaluation of pelvic floor, and established as alternative to conventional defaecography (evacuation proctography) in many institutions. Examination should include MRI at different pelvic positions (at rest, during squeezing, at straining, and during evacuation). Rectal enema necessary. See Fig. 2.2.

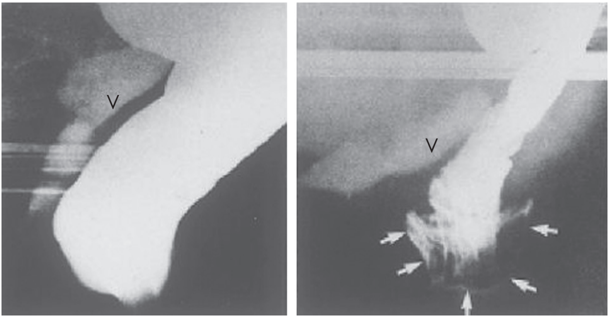

Fig. 2.2 Defaecating proctogram showing rectal intussusception. Left, normal rectum prior to defaecation. Right, attempted defaecation leads to intussusception.

Reproduced from Feldman M, Friedman LS, and Sleisenger MH (2003). *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, with permission from Elsevier.

Nuclear medicine

Positron emission tomography (PET) scanning

Most tumour imaging relies on demonstrating abnormal anatomy (e.g. a mass). PET provides information on function, usually relying on ↑ metabolic rate common to most malignancies (using glucose analogue [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) as tracer), but sometimes using other radioligands that bind to specific receptors. Combining PET with CT or MRI allows functional and anatomical assessment.

Indications

- In GI disease, increasing role for PET-CT/MRI in primary staging of ➲ colon cancer and ➲ oesophageal cancer, particularly identification of metastases.
- As well as primary staging, PET-CT in ➲ colon cancer is used for:
  - Differentiating local recurrence from post-treatment changes.
  - Excluding extrahepatic metastases in patients with apparently isolated (and therefore resectable) liver recurrence post-primary tumour resection.
  - Identifying site of recurrence in patients with rising tumour markers, and no sign of recurrence on anatomical imaging.
- No routine role for PET in staging of ➲ pancreatic cancer or distinguishing benign from malignant pancreatic disease.
- FDG of limited use in diagnosing and staging of ➲ carcinoid and ➲ pancreatic endocrine tumours, probably because of lower metabolic rate, but other tracers (e.g. [^{11}C]L-dopa, [^{11}C]5-HTP, [^{68}Ga]octreotate (see ➢ 'Octreotide scanning', see below)) widely used.

Limitations

- Differentiation of reactive and malignant lymph nodes difficult.
- False-negatives in tumours with low metabolic rate.
- False-positive uptake in colon (although may sometimes be first indication of undiagnosed colitis or colonic polyps).
- May fail to characterize lesions <1cm.

Octreotide scanning

Also known as somatostatin receptor scintigraphy (SRS), utilizes radioactive octreotide (somatostatin analogue) to find carcinoid and other ➲ neuroendocrine tumours. Intravenously injected [^{111}In]octreotide attaches to cells that have somatostatin receptors and identified using γ camera. [^{68}Ga]Octreotate PET may enhance yield when results from octreotide scan equivocal.

Meckel's scan

[^{99m}Tc]pertechnetate scan is the investigation of choice to diagnose Meckel's diverticula. Detects gastric mucosa. As 50% of symptomatic Meckel's diverticula contain ectopic gastric or pancreatic cells, this is displayed as a hotspot on scan distant from stomach itself.

Red cell scan

RBCs can be removed from patient, labelled with ^{99m}Tc, then re-injected to localize site of GI bleeding to guide treatment. In general, however, the yield is low. Rate of bleeding affects result, but patients with higher rates are unstable and the risk of taking them through this procedure usually outweighs benefits. Now largely superseded by ➢ angiography (CT and direct), and ➢ video capsule endoscopy.

White cell scan

Labelling of granulocytes or mixed leucocyte populations with ^{99}Tc or ^{111}In used for many years to investigate and localize inflammatory processes involving abdomen or bowel. Less used since advent of non-invasive tests such as faecal calprotectin and improved functional imaging with ➢ PET. Time consuming: labelling takes 2h, with re-injection of labelled cells and imaging performed 24h later.

Bone densitometry (see also ➲ osteoporosis)

Method of measuring bone mineral density (BMD) to detect osteopaenia or ➲ osteoporosis. Can be expressed as number of standard deviations (SD) above or below mean BMD for young adults (T score), or mean BMD for age-matched controls (Z score). Risk of fracture ↑ 2–3× for each SD decrease in BMD. WHO criteria for defining osteoporosis: T score in hip and/or spine ≥2.5× SD below young adult mean value, and osteopaenia is T score 1–2.5 SD below mean. Best technique involves dual-energy X-ray absorptiometry (DEXA). Note that lumbar spine measurements unreliable in elderly because of presence of osteophytes, extraskeletal calcification, and vertebral or spinal deformity. See also Box 2.12.

Box 2.12 Guidelines for DEXA scanning in GI patients

- Patients with 2 or more of:
  - Continuing active disease (particularly ➲ coeliac disease and ➲ inflammatory bowel disease).
  - Weight loss >10%.
  - BMI <20.
  - Age >70.
- Patients <65y requiring steroids (≥7.5mg prednisolone equivalent) for >3mo. DEXA should be repeated annually until steroids stopped or intervention threshold (e.g. T score <1.5) reached.

Angiography

- Radiological visualization of blood vessels after injection of radio-opaque contrast. May be performed using serial focused X-rays, CT, or MRI. Can be diagnostic and therapeutic (see ➢ Embolization).
- Most frequent use in GI patients is for upper or lower GI bleeding where source not readily identified on initial endoscopy (see ▲ **acute upper gastrointestinal bleeding** ▲ and ▲ **acute lower gastrointestinal bleeding** ▲).
  - Bleeding rates >0.5ml/min can be detected with selective catheter angiography.
  - CT and MRI not as sensitive (typically require brisker bleeding to visualize), but less invasive and can help plan subsequent targeted selective angiography. Also have advantage of visualizing tissues, enabling detection of other pathologies.

Embolization

- Arterial embolization leads to obstruction of distal flow. Usually achieved through placement of intraluminal coils. Indications: acutely bleeding posterior duodenal ulcers (due to gastroduodenal artery (GDA)), pseudo-aneurysm related to ➲ pancreatic pseudocyst (often splenic artery). colonic ➲ angiodysplasia, or post-polypectomy bleeds (branch of superior or inferior mesenteric arteries).
- Malignant tumours are often hypervascular, so embolization may ↓ tumour load due to ischaemia/infarction (e.g. embolization of branch of hepatic artery in patients with hepatocellular carcinoma).
- Selective ipsilateral portal vein embolization in patients with ➲ hepatocellular carcinoma (HCC) or liver metastases from ➲ colonic cancer may produce compensatory hypertrophy of contralateral liver lobe, providing sufficient liver reserve to allow hemihepatectomy and tumour resection. Transarterial chemoembolization also has role in management of unresectable HCC.

Important complications include vascular compromise of surrounding tissue: duodenal ulceration/stricture following GDA embolization; liver infarction, and ▲ **acute liver failure** ▲ following hepatic artery embolization (particularly in patients with ➲ portal vein thrombosis and those with ➲ Child–Pugh score B/C). Biliary sepsis/➲ liver abscess formation also a risk, particularly if embolization performed in setting of pre-existing biliary obstruction.

Screening and surveillance for GI malignancy

Definitions

- **Screening** is the one-time application of a test that allows detection of disease at a stage when intervention may significantly improve the natural course and outcome.
- **Surveillance** is repeated application of such a test over time.

The GI tract, including the hollow organ of the gut, liver, pancreas, and biliary tree, is the site of more cancers than any other organ system, and more people die of cancers of the GI tract than those of any other organ. While there is no simple common cause of GI tumours, and wide variability in tumour incidence between countries, there are some common principles of screening:

- High-risk groups can be identified for several cancers.
- Morbidity and mortality are often ↓ by early diagnosis, ideally in asymptomatic individuals.

Surveillance involves monitoring people with previous GI neoplasia or premalignant conditions with the objective of preventing cancer. Some GI tract cancers are so common that screening of the general population at average risk of cancer is performed (see ➢ ‘colon cancer screening’, p. 172).

People at increased risk of digestive tract cancer

- Family or personal history of neoplasia (best established for ➲ colorectal cancer).
- Genetic syndromes predisposing to cancer.
- Other conditions of GI tract associated with ↑ risk of cancer (e.g. ➲ inflammatory bowel disease).
- Other diseases associated with ↑ risk (e.g. ➲ acromegaly).

Oesophagus

Screening

Adenocarcinoma

No screening programmes worldwide for general population. Screening focused on detecting ➲ Barrett’s oesophagus through diagnostic endoscopy with subsequent surveillance. No evidence to screen families with history of either adenocarcinoma or Barrett’s oesophagus.

Squamous carcinoma

Screening indicated in:

- ➲ Tylosis (genetic defect in *RHBDF2*, found in patients with thickened palms and soles). Patients often develop cancer by age 65.
- ➲ Caustic strictures (8% incidence of cancer 45y after ingestion).
- Long-standing ➲ achalasia.
- Patients with history of oral cancers are recommended to have endoscopy with Lugol’s ➢ chromoendoscopy should they be undergoing a diagnostic procedure, due to ↑ incidence of squamous dysplasia/carcinoma,.

- Excess alcohol consumption in some Asian patients.
- Screening for squamous cell cancer effective in high incidence areas such as northern China, where 5y survival approaches 90% for cancers detected through screening.

Surveillance

Incidence of cancer in ➔ Barrett's oesophagus low in general (5–10% lifetime risk) so surveillance is only cost effective in at-risk populations. Dysplasia currently used to identify at-risk patients.

Biopsy protocol for dysplasia

Make sure patients are free from oesophagitis, as dysplasia is difficult to assess in presence of inflammation. Take 4 quadrantic biopsies every 2cm of Barrett's mucosa, starting at gastro-oesophageal junction and stopping at the squamocolumnar junction. Patients with mucosal abnormalities should undergo endoscopic mucosal resection and/or ablation to eliminate neoplasia.

Methods of surveillance

- At present, no alternatives to biopsy, although trials exploring use of brush cytology and diagnostic optical imaging techniques such as spectroscopy and confocal laser endomicroscopy.
- Recommended that thorough inspection of oesophagus, including use of optical enhancement techniques, ➢ chromo-endoscopy, and magnification endoscopy utilized prior to taking biopsies. Areas of concern should be targeted with biopsy prior to the random 4 quadratic biopsies are taken.
- Cytology is an accepted practice for screening in high-risk areas, although not in Western populations.
- ➢ Chromoendoscopy with acetic acid in the surveillance of ➔ Barrett's oesophagus is recommended, with lack of aceto-whitening 92% sensitive and 96% specific for dysplasia. Lugol's iodine has been used in screening for squamous cancer: unstained areas 90–100% sensitive and 40–90% specific for dysplasia or cancer.
- Magnification endoscopy enhances mucosal detailing and often used with chromoendoscopy.

Significance of dysplasia

Annual risk of progression to cancer 0.4% in patients without dysplasia, compared with 14% with low-grade and 22% with high-grade dysplasia. Unfortunately, classification of dysplasia is subjective and agreement between at least 2 pathologists should be sought. Surveillance can ↑ survival. Nodal involvement affects prognosis and is less likely in surveyed than in non-surveyed patients.

Frequency of surveillance

Outlined by national guidelines. Patients with non-dysplastic Barrett's oesophagus should have periodic surveillance every 2–5y, depending on length of Barrett's oesophagus (more frequent surveillance not cost effective). Patients with low-grade dysplasia should be offered treatment to eliminate the dysplasia; should this be declined then annual surveillance suggested, provided patient will benefit from being in a surveillance programme. Patients with high-grade dysplasia should have definitive endoscopic or surgical management. Patients with dysplasia should be referred to specialist centre for ongoing care.

Stomach

Countries with high risk have screening programmes, although exact nature varies. Even within Japan, different approaches taken in different regions. Screening can range from endoscopic surveillance, use of serum pepsinogen markers, or even double-contrast radiography of general population (picks up 12 cases/10,000 screening exams). Screening programme in Japan has led to significant improvements in gastric cancer prognosis, with many patients undergoing endoscopic resection of premalignant or early malignant lesions. No evidence of any difference in tumour biology in Japan compared with Europe (infection with ➲ *H. pylori* remains main causative agent).

Within lower risk countries, including UK, 3 yearly endoscopic surveillance of patients with moderate/severe atrophic gastritis recommended, with those found to have dysplasia or cancer being offered therapy (including endoscopic resection). Further studies exploring use of biomarkers (including pepsinogen) for screening general population underway. Others recommended to undergo surveillance include those with previous history of surgical gastric resection (remnant stomach at 2–4-fold ↑ risk of ➲ gastric cancer), and those with syndromes linked to gastric cancer (including ➲ familial adenomatous polyposis).

Pancreas (see ➲ pancreatic adenocarcinoma)

- Hereditary factors play role in 5% of newly diagnosed cases. Predisposing genetic disorders include ➲ multiple endocrine neoplasia, ➲ hereditary non-polyposis colorectal cancer, ➲ familial adenomatous polyposis, and von Hippel–Lindau syndrome.
- ➲ Hereditary pancreatitis (associated with *PRSS1* mutation) and familial pancreatic cancer (10–20% of patients have *BRCA2* mutation) carry 40% lifetime risk of pancreatic carcinoma.
- Screening programmes being defined for high-risk groups and include genetic analysis, with baseline CA19-9 and imaging (EUS + CT and MRI), and 1–3-yearly imaging thereafter.
- Screening of general population not established.
- Urinary metabolite panels still in research stages.

Liver and biliary tract

➲ *Hepatocellular carcinoma (HCC)*

- Definitive evidence for survival benefit from screening for HCC lacking, but very poor prognosis for symptomatic tumours (5y survival 0–10%). Good results for lesions amenable to resection (i.e. smaller) suggest benefit.
- All patients with cirrhosis should be screened, as annual incidence of developing HCC 1–6% and account for vast majority of cases (although 20–50% of patients with HCC have previously undiagnosed cirrhosis).
- Chronic ➲ hepatitis B carries high risk of HCC, even in absence of cirrhosis. Risk directly related to HBV viral load.
- Most screening and surveillance programmes combine measurement of serum ➢ αFP and hepatic US every 6 months..
- αFP >100g/L in high-risk groups has specificity of 99%, but relatively poor sensitivity at 31% (hence some screening programmes now exclude αFP measurement).
- Sensitivity of US for tumours >1cm is 95%.
- Surveillance intervals vary, but 6-monthly reasonable given average tumour doubling time of 4–6 months.

➲ *Cholangiocarcinoma*

- Chronic biliary inflammation is the main risk factor, e.g. ➲ primary sclerosing cholangitis, ➲ choledochal cyst, chronic parasitic infection (e.g. ➲ clonorchis).
- No verified screening programme established. Tumour markers (e.g. CA19-9), CT/MRI, and invasive testing at time of biliary endoscopy (e.g. biliary cytology) often adopted in PSC. Raised CA19-9 has high false-positive rate in setting of biliary obstruction.

➲ *Gallbladder carcinoma*

- ➲ Gallstones, ➲ primary sclerosing cholangitis, ➲ gallbladder polyps >1cm, and calcified (porcelain) gallbladder are all risk factors (prophylactic cholecystectomy usually advised for latter two).
- Screening in patients with gallbladder stones not indicated.
- Yearly US in patients with PSC advocated, with cholecystectomy if any evidence of polyps (however small).

Colorectal

Colorectal cancer (CRC) screening

Average risk (i.e. background population risk, no risk factors present):

- Two screening modalities ↓ mortality from colon cancer:
  - ➢ FOBT. Up to 30% ↓ in mortality if done annually with rigorous follow-up of positive results with endoscopy. FIT provides quantitative measure of Hb in stool, and is expected to replace FOBT.
  - Endoscopic examination of colon.
- ➲ CT pneumocolon/faecal tagging are both acceptable for screening, but do not allow biopsy or removal of lesions. CT >95% sensitive at detecting polyps >5mm. Although smaller lesions may be missed, these are extremely unlikely to be malignant.
- Different programmes for screening exist using faecal occult blood screening, limited or full colonoscopies, and different imaging regimens. In UK, screening of average risk people for colon cancer using FOBT began in 2006. The **bowel scope programme** rolled out one-time flexible sigmoidoscopies for all people over age of 50 (<2% of people with a normal sigmoidoscopy have proximal tumours).[10] Currently relative merits of bowel scope and FIT being evaluated, which may change screening policy.

Increased risk

- Family history (excluding familial cancer syndromes). Familial clustering of colorectal cancer is common. Risk ↑ depending on number of affected relatives, their age of diagnosis, and presence of adenomatous polyps in 1st-degree relative <60y (Table 2.4). How this affects screening is controversial and depends on cut-off of acceptable risk, but in general screening with 2-yearly FOBT and 5-yearly colonoscopy (many tumours right-sided) is recommended. Patients with many affected family members or with an affected 1st-degree relative aged <55y should have colonoscopy 10y earlier than the earliest cancer occurred in the family.
- Cancer family syndromes: genetic screening is valuable for syndromes related to ➲ familial adenomatous polyposis (FAP). Referral to a geneticist should be considered if the history is not definitive.

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[10] Imperiale TF *et al.* (2000). *N Engl J Med* **343**: 169–74.

Table 2.4 Familial colon cancer: risk

Relatives affected	Risk
None	1 in 35
One 1st-degree	1 in 17
One 1st-degree and one 2nd-degree	1 in 12
One 1st-degree under 45y	1 in 10
Both parents	1 in 8.5
Two 1st-degree	1 in 6
Three 1st-degree	1 in 2

Colorectal cancer surveillance (see Table 2.5)

High risk

- Highly penetrant autosomal dominant syndromes:
  - ➲ familial adenomatous polyposis.
  - ➲ hereditary non-polyposis colorectal cancer.
- Hamartomatous polyposis syndromes (➲ Peutz–Jeghers syndrome, juvenile polyposis, ➲ Cowden's disease; see Plate 7).
- Long-standing history of ➲ inflammatory bowel disease of colon.
- Patients with ➲ acromegaly. Current recommendations are for 3-yearly colonoscopy from age 40.

Table 2.5 Screening recommendations for familial colorectal cancers

Condition	Recommendation
➲ Familial adenomatous polyposis	Genetic testing for APC mutations at age 12. Yearly flexible sigmoidoscopy starting at age 12 if family history of FAP. If polyps found, full colonoscopy with view to prophylactic colectomy and surveillance of remaining rectum. In addition, upper endoscopic surveillance of stomach, duodenum, and periampullary region. Consider αFP for hepatoblastoma.
➲ Hereditary non-polyposis colorectal cancer	Individuals identified by family history (see Amsterdam criteria in ➲ hereditary non-polyposis colorectal cancer). Start colonoscopic surveillance (***not*** flexible sigmoidoscopy, because many tumours right-sided) at 20–25y at intervals of 1–2y. Offer genetic testing to 1st-degree relatives of patients with known inherited mismatch repair defect.
➲ Peutz–Jeghers syndrome	2-yearly upper and lower GI endoscopy, with intermittent MRI ➢ enteroclysis or ➢ capsule endoscopy). Polypectomy for large polyps to avoid intussusception. Surveillance for gonadal, breast, cervical cancer.
➲ Juvenile polyposis	Rare. No firm guidelines.

Moderate risk

- Prior history of adenomatous colonic polyps:
  - Solitary adenomas <1cm diameter do not predict recurrent neoplasia and do not need follow-up.
  - Surveillance colonoscopy indicated for adenomas >1cm; villous/tubulovillous histology; multiple adenomas; and advanced dysplasia.
  - 3y interval adequate for follow-up colonoscopy if colon has been cleared of polyps, with subsequent intervals of 5y.
- Prior history of colon cancer
  - Anastomosis site should be examined at 3–6mo and perhaps again at 1y (little evidence for this recommendation).
  - After this, examination recommended every 3–5y as for patients with advanced adenomas.
- Inflammatory bowel disease. See Box 2.13.

Box 2.13 Colorectal cancer surveillance in patients with inflammatory bowel disease

Extensive ➲ ulcerative colitis or ➲ Crohn's colitis of >10y have ↑ risk of colon cancer. Magnitude varies in different studies, partly due to referral bias reflecting hospital rather than community prevalence studies. Commonly quoted figures are 7–15% at 20y after diagnosis of UC, increasing ~1%/y after this. Long-term treatment with 5-ASA ↓ risk. Risk is further ↑ in patients with:

- ➲ Primary sclerosing cholangitis.
- Family history of ➲ colon cancer.
- (Possibly) young onset of disease.
- Colonic stricturing.

Some data to suggest endoscopic surveillance improves mortality from colon cancer in IBD, though quality of evidence low (see Cochrane review, 2017. 🔗 https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000279.pub4/full). Areas of dysplasia are difficult to see macroscopically. Previous guidelines recommended surveillance with colonoscopic biopsies taken from four quadrants every 10cm. New guidelines emphasize very low pick-up of dysplasia in random biopsies and recommend use of ➢ chromoendoscopy to identify abnormal mucosa with subsequent mucosal resection or biopsy. Guidelines also emphasize differentiating sporadic adenomas arising in colitic colon (which can be removed in normal way) from dysplasia-associated lesions or masses (DALMs) that mandate colectomy.

Follow-up post-polypectomy

About 30% of people undergoing colonoscopic polypectomy will develop recurrent adenomas (although any lesion missed at index examination will be considered a recurrence). Main risk factor is presence of multiple adenomas at index examination. Less important factors are polyp size over 10mm, advanced age, and villous histology.

Frequency of surveillance colonoscopy

See Rutter, Gut 2020.[11] High risk criteria for developing future CRC include;

- 2 or more premalignant polyps, including at least 1 advanced polyp (serrated polyp at least 10 mm or containing any degree of dysplasia, or an adenoma of at least 10 mm or containing high-grade dysplasia)
- 5 or more premalignant polyps

This cohort should have one-off surveillance colonoscopy at 3y. Post CRC resection patients should have 1y clearance colonoscopy, then a surveillance colonoscopy after 3 more years.

Effect of family history on polyp surveillance

- No evidence to suggest recommendations differ for patients with family history found to have adenoma, unless dominantly inherited family syndrome suspected.

Stopping surveillance

- In patients over age 75, it is unlikely the benefits of surveillance outweigh risks of procedure. However, patient fitness and motivation affect age cut-off for stopping surveillance.

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[11] Matthew D Rutter *et al*. (2020). British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England post-polypectomy and post-colorectal cancer resection surveillance guidelines. **69**(2):201–223.

Bedside procedures

Nasogastric tubes

Indications

- Decompression of stomach (with aspiration of gastric contents) in gastric outlet or small bowel obstruction.
- Reduction of risk of aspiration pneumonia in at-risk patients (e.g. prolonged vomiting, ↓ conscious level).
- Provide temporary (usually <4wk) nutritional support in patients with functioning GI tract but who cannot (or, in certain circumstances, will not) eat. Longer periods of enteral nutrition can be provided by ➤ percutaneous endoscopic gastrostomy (PEG) tube placement (see p. 205).
- Fine-bore (5–8Fr) silicone or polyurethane tubes generally used for feeding, but tubes for gastric decompression or drainage larger (Ryles tubes, 12–14 Fr).

Technique

See Box 2.14 for procedure for inserting NG tube.

Complications

- During insertion: nasal damage, intracranial insertion (risk in patients with skull fractures), oesophageal pouch perforation, bronchial placement.
- Post insertion: erosive tissue damage, strictures, discomfort, displacement, reflux (aspiration/oesophagitis), ➲ refeeding syndrome.
- Tube occlusion with inspissated feeds or crushed medications.

Box 2.14 Inserting nasogastric tube

- Explain procedure to patient and gain informed consent.
- Mark tube at distance equal to that from xiphisternum to nose via ear lobe (usually 50–60cm).
- If feasible, ask patient to 'sniff' while occluding other nostril, and choose clearest. Spraying nostril with lidocaine may ↓ discomfort.
- Sit patient upright, or at least at 45°, if possible.
- Lubricate tube and slide gently along floor of nostril.
- After 10–15cm (tip may be visible at back of pharynx) ask patient to swallow mouthful of water (if appropriate), and advance tube 5–10cm as they swallow. Repeat until preset distance reached.
- Withdraw tube if patient distressed, coughing, or cyanosed.
- Once tube in place, remove guidewire. Tape to nose and side of face.
- To confirm appropriate position, at a minimum use pH indicator paper to check aspirated fluid has pH <5.5. Higher pH suggests position wrong (or patient may be on proton pump inhibitor). If pH >5.5, position must be checked using CXR. ❗ Many hospitals now mandate radiological confirmation of correct placement before use, even if alternative methods suggest this has been achieved.

Paracentesis

Drainage of fluid from peritoneal cavity (see ► Approach to ascites). Most common indication is diuretic-resistant ascites related to ➲ portal hypertension, but other causes include malignant ascites. ➲ TIPSS occasionally performed as an alternative to recurrent paracentesis.

Technique

- As with most procedures in medicine, the best way to perform safely and effectively is to watch and learn from experienced colleagues.
- In non-cirrhotic patients, ensure clotting is optimized prior to drainage (e.g. INR <1.5, platelets >50 × 10^9/L). However, in cirrhotic patients, normalisation of clotting is likely to be impossible and standard practice is not to attempt INR correction.
- Patient supine or with head of bed elevated ~30°.
  - Traditional method was to examine the abdomen, particularly noting lower margins of liver and spleen, then moving laterally from the umbilicus, percuss into the flanks until area of stony dullness reached (usually anterior axillary line). On rolling patient, confirm that the area of dullness is related to fluid (see ➢ 'Gastrointestinal examination', p. 130). Use hub end of needle to mark site of planned needle insertion.
  - However, now, US-guided drain insertion is recommended whenever possible.
- Perform under sterile conditions (i.e. wear sterile gloves + gowns; sterile drapes around 'surgical field'). Clean around insertion point with chlorhexidine (>8cm radius). Using a 22G needle and 5ml syringe, raise a subcutaneous bleb with lidocaine 2%, then inject further anaesthetic through skin until peritoneal cavity reached (confirmed by aspiration of ascites). Using a 20ml syringe, send fluid for analysis (see ► Approach to ascites and ➲ spontaneous bacterial peritonitis). Using a pointed-tip scalpel, make 5mm incision through skin. Insert drainage catheter over trocar at 90° to skin. Depending on patient adiposity, peritoneal cavity entered 4 cm from skin, often indicated by ascitic fluid seeping back along catheter. At this point, advance further 1cm, then withdraw trocar while advancing catheter (should occur without resistance or discomfort). Tape catheter securely to skin (no need to stitch) and attach drainage bag to catheter. Keep bag below level of patient and leave on free drainage.
- Reduced circulating blood volume, with secondary hyperaldosteronism and sympathetic drive, may occur 12–24h after large paracentesis (e.g. 4–6L). To prevent this, most hepatologists advise use of albumin as plasma expander in transudative ascites (e.g. give 100ml 20% human albumin solution (HAS) after every 2L drained). No logic in giving albumin infusion in malignant ascites (as serum–ascites albumin gradient is low).
- Drain should be removed within 6h, or when the agreed amount of ascites has been drained.
- Rare complications include intraperitoneal bleeding, bowel perforation (particularly if history of abdominal surgery, i.e. possible adhesions), and infection (secondary bacterial peritonitis).

Liver biopsy (LBx)

- No investigation should be performed unless result might change management. LBx demonstrates this point *par excellence*, altering patient management in only 30% of cases. However, LBx does have central role in evaluating a wide range of liver diseases.
- Recent development of commercially available blood markers and US systems to assess liver fibrosis is ↓ need for LBx (see Box 2.16).

Indications

- Chronic viral ➲ hepatitis B and C: histological grade (inflammation) and stage (fibrosis) may determine need/timing of treatment.
- Unexplained hepatitis/abnormal LFTs: where non-invasive tests, such as serology, are non-diagnostic. See also ► Approach to well patients with abnormal liver tests.
- ➲ Autoimmune hepatitis: during initial work-up, and probably in assessing treatment response.
- ➲ Non-alcoholic fatty liver disease (NAFLD): LBx only way of differentiating NAFLD from non-alcoholic steatohepatitis (NASH), which may show histological progression. Selection of patients with NAFLD who should be biopsied has not been clearly defined.
- ➲ Alcoholic liver disease: especially exclusion of ➲ alcoholic hepatitis, as clinical diagnosis wrong in 20% of cases.
- Focal liver masses: liver metastases, ➲ focal nodular hyperplasia, ➲ hepatocellular carcinoma. LBx may be avoided where imaging diagnostic, and when needle-track seeding may significantly affect prognosis (see 'Contraindications to percutaneous LBx').
- Routine use of LBx, where diagnosis has been established by other modalities, remains unclear for ➲ primary biliary cholangitis, ➲ primary sclerosing cholangitis, and ➲ Wilson's disease. Rarely needed in proven acute viral hepatitis.

Contraindications to percutaneous LBx

- Uncooperative patient (sudden movement risks liver laceration).
- Biliary obstruction: ➲ cholangitis.
- Deranged clotting: usual advice is to avoid percutaneous LBx if INR >1.3 (i.e. PT prolonged >3s), but little clear data and 90% of biopsy-related bleeds occur in patients with INR <1.3. If INR 1.4–1.6, may give FFP, and perform LBx if INR reduces to <1.4. If coagulopathy present and cannot be corrected sufficiently to allow safe percutaneous LBx, consider transjugular LBx.
- Low/dysfunctional platelets: minimum safe lower limit of platelets 60×10^9/L for percutaneous LBx (but recommendations vary). If platelets 40–60×10^9/L, LBx may be performed immediately after platelet transfusion, if count ↑ to 'safe' level. Bleeding time should be considered in patients with suspected impaired platelet function (e.g. renal failure, recent antiplatelet drugs), as bleeding time >10min associated with ↑ risk of bleeding.
- Significant ascites: drain ascites first (see ➢ paracentesis), but transjugular LBx is alternative.
- ➲ Amyloidosis and sickle-related hepatopathy: historical data suggest ↑ risk of intraperitoneal bleeding.

- Cystic liver lesions: if communicate with biliary tree biopsy may precipitate biliary leak. Risks of anaphylaxis if inadvertent biopsy of ➔ hydatid cyst.
- Confirmatory LBx generally avoided in presumed resectable ➔ hepatocellular carcinoma as risk of needle-track seeding (but reported incidence from diagnostic LBx <2%).

Pre-procedure care

- Written informed consent.
- Stop antiplatelet medication at least 1wk prior to procedure, if clinically possible. Take advice if uncertain (e.g. in patients on clopidogrel with coronary stents). Anticoagulation must be stopped prior to percutaneous LBx.
- Pre-procedure blood tests, as discussed earlier (within last 2wk if stable chronic disease; more recent if change likely, e.g. recent-onset jaundice).
- Imaging. US or CT liver essential prior to LBx, in part to exclude unexpected pathology that may ↑ risks (e.g. intrahepatic gallbladder, liver cyst). Debate continues as to whether ‘untargeted’ LBx should be performed under US guidance in all cases (as argued by most radiologists).

Technique

See Box 2.15 for procedure for performing liver biopsy.

Complications/risks

Mortality 0.1–0.3%, morbidity 5.9%. Complications and death most commonly related to intraperitoneal bleeding or peritonitis following gallbladder perforation. Risk factors for bleeding include ↑ patient age, intrahepatic malignancy, and >2 needle passes. Puncture of lung (pneumothorax), colon, and kidney all recognized. Small subcapsular haematomas seen on US in >20%, but rarely symptomatic.

Box 2.15 Liver biopsy procedure

- Patient lies supine, with right hand behind head.
- Liver identified by percussion or (ideally) US. Usual approach in mid-axillary line, between lower ribs.
- Aseptic technique. Clean skin with chlorhexidine-based solution.
- Infiltrate down to liver capsule using 22G needle and 4–6mL lidocaine 1–2%. Line of infiltration just above edge of lower rib (to avoid neurovascular bundle running on underside of upper rib).
- 5mm scalpel cut into skin to allow advancement of biopsy needle.
- Biopsy performed with patient having been instructed to stop breathing after full expiration (raises diaphragm, thus reducing risk of pneumothorax).
- Two types of biopsy needle used: cutting needle (e.g. Trucut) provides good cores of tissue, but may carry slightly higher complication rate than suction needle (e.g. Menghini). Important those undertaking LBx gain confidence and experience using one type.
- After biopsy, patient lies in right lateral position for 1h (helps 'tamponade' liver capsule against chest?), then supine for 2h, and stays in hospital for 6h. Vital signs monitored every 15min for 2h, then every 30min for 2h, and then hourly (>80% of complications occur within first 10h, and 60% within 2h).

Guideline

BSG Guideline on Use of Liver Biopsy (2020). 🖰 https://www.bsg.org.uk/wp-content/uploads/2020/06/gutjnl-2020-321299.full_.pdf.

Box 2.16 End in sight for liver biopsies?

Non-invasive means of assessing liver inflammation and fibrosis, without risks of biopsy, are actively sought. Serum marker panels assess blood biomarkers that reflect deposition and removal of extracellular matrix (e.g. α_2-macroglobulin, apolipoprotein A1). Commercial kits include Fibrotest™ and Enhance Liver Fibrosis (ELF)™. Fibroscan™ assess liver stiffness by means of US probe that analyses velocity of shear wave passed through liver tissue. Limitations in markedly obese patients (although new probes available). These non-invasive tests appear to correlate well with liver biopsy where there is significant fibrosis/cirrhosis, but are less predictably for mild liver injury. They do not provide any indication of aetiology.

Surgery

Antireflux procedures

Range of mechanical interventions available for patients with persistent problems related to ➲ gastro-oesophageal reflux disease (GORD) despite maximal medical therapy (see ► Approach to dyspepsia and gastro-oesophageal reflux). Aim to reverse mechanical and physiological abnormalities of GORD, which should be proven by ➢ oesophageal manometry. Endoscopic and surgical options available.[12]

Endoscopic approach

- Approaches include radiofrequency heat treatment, transoral fundoplication, and antireflux resection of the GOJ.
- **Stretta system** delivers radiofrequency energy to GOJ. Large prospective series demonstrate sustained improvement in GORD symptoms, quality of life, and PPI therapy elimination. Sham-controlled study showed improvement in symptoms at 6mo.
- **Transoral incisionless fundoplication** performed with EsophyX device, to obtain partial gastroesophageal valve comparable to principles of Nissen fundoplication. Improvements in symptoms demonstrated in two randomized controlled trials.
- Stapling and suturing approaches met with limited success. Infrequently used, and some devices no longer available.

Surgical approach

- **Nissan fundoplication** performed laparoscopically or as open operation (Box 2.17). Involves mobilization of lower oesophagus, reduction of hiatus hernia, and wrapping of gastric fundus around lower oesophagus, either totally (e.g. Nissan 360° fundoplication; Fig. 2.3) or partially (e.g. Toupet 270° fundoplication). Re-establishes competence of antireflux barrier and ↑ resting lower oesophageal sphincter pressure. Complications include dysphagia and air trapping, which may require re-operation, and reported in >10% following laparoscopic fundoplication. Mortality rate of 0.2% of significance in condition that runs benign course in majority. No good evidence surgical fundoplication ↓ risk of ➲ oesophageal tumours.
- **EndoStim®** enhances LOS function by laparoscopic implantation of electrodes anteriorly at GOJ, with generator implanted in abdominal wall. Longitudinal registry data demonstrate ↓ distal oesophageal acid exposure and improved symptoms.
- **LINX® Reflux Management System** augments LOS through magnetomechanical resistance against expansion. Deployed laparoscopically at GOJ. Prospective longitudinal studies demonstrate ↓ oesophageal acid exposure, GORD symptoms, and PPI use.

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[12] Nicolau AE *et al.* (2018). *Chirugia* **113**: 70–82.

Patient selection for surgery difficult, but indications may include:

- Failed medical therapy, with persistent symptomatic ➲ oesophagitis.
- Young healthy patient who responds to medical therapy, but unable/unwilling to take long-term medication.
- Recurrent reflux complications (e.g. laryngitis, asthma, pneumonia).

Box 2.17 Surgical fundoplication: open or laparoscopic approach?

Meta-analysis concluded laparoscopic antireflux surgery (LARS) effective and safe alternative to open surgery for treatment of proven GORD. Faster convalescence and return to productive activity, with ↓ complications than open approach. However, significantly ↑ rate of re-operation (79%) in LARS group.[13]

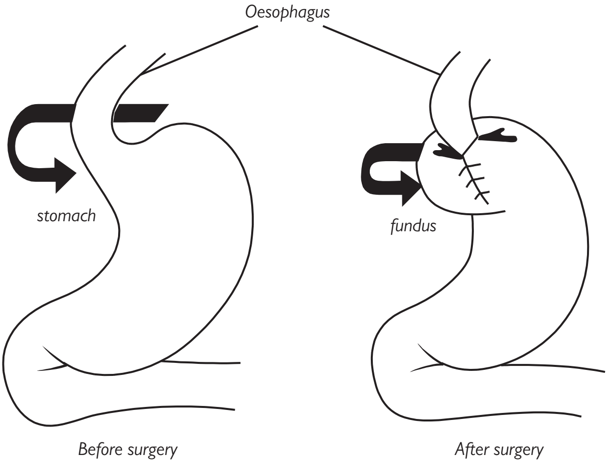

Fig. 2.3 Nissan fundoplication

Anti-obesity (bariatric) surgery

Bariatric surgery is now one of the most common surgical procedures in the USA, and use also increasing year-on-year in UK. Proven benefit in reducing weight in morbid obesity (20% ↓ expected), with benefits for cardiovascular risk, diabetes, lipids, and ➲ non-alcoholic fatty liver disease. Various procedures established, including:

- ***Gastric bypass*** Transection of proximal stomach, with jejunal loop anastomosed to gastric remnant/distal oesophagus and Roux-en-Y anastomosis formed. Weight loss occurs partly due to gastric diversion causing malabsorption and partly due to ↓ gastric volume.

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[13] Peters MJ *et al.* (2009). *Am J Gastroenterol* **104**: 1548–61.

- *Gastric banding* Laparoscopic band applied to gastric fundus, restricting gastric volume, resulting in early satiety.
- *Sleeve gastrectomy* Stapling/resection of greater curve of stomach to anatomically ↓ gastric volume.

Over 95% of these procedures now performed laparoscopically. Surgical mortality <0.01%, but complications in 20–40% including ➲ dumping syndrome, intestinal obstruction, dysphagia, steatorrhoea/diarrhoea, infection, gallstones, and herniae.

Oesophagectomy

Surgical resection with potential for cure remains mainstay of treatment for ➲ oesophageal cancer. Most common approach via laparotomy and right thoracotomy (Lewis–Tanner operation). Early complications include anastomotic leakage (0–13%), pulmonary problems including pneumonia and PE (6–50%), recurrent laryngeal nerve injury (1–13%), and cardiac problems. Reported mortality 1–13% with 5y survival 1–35%, although when survival data are stratified for tumour staging, node-negative tumours are associated with 5y survival of ~50%, highlighting potential rewards with early diagnosis.

Transhiatal oesophagectomy has theoretical advantages through avoiding complications of thoracotomy, but comparative studies have failed to show any advantages over traditional techniques. In addition, transhiatal approach does not allow complete lymph node removal.

Development of minimally invasive surgery allows thoracoscopic and mediastinoscopic mobilization of oesophagus, with claims adequate lymphadenectomy can be performed. Evidence suggests comparable morbidity and mortality to conventional approach. Organ used to replace oesophagus can be stomach, colon, or jejunum.

Gastrectomy/gastroenterostomy

- *Total gastrectomy* involves anastomosis of jejunum to distal oesophagus, after gastric resection. Usual indication: malignancy. Surgery is the only curative procedure for ➲ gastric cancer and also useful for palliation of symptoms, especially obstruction. Roux-en-Y anastomosis also required.
- *Partial gastrectomy* now rare, but was common treatment in past for ➲ peptic ulceration. Emergency surgery still needed, largely when perforation or catastrophic bleeding is the first manifestation of disease. Subtotal gastrectomy to remove source of gastrin and parietal cell mass has high rate of complications and now reserved for treatment of uncontrollable haemorrhagic gastritis and gastric cancer. Billroth I operation involves directly joining gastric remnant onto duodenum; Billroth II involves closing duodenal stump and making gastroenterostomy. Billroth I preferred as lower incidence of ➲ dumping and weight loss. Billroth II used if duodenal inflammation makes Billroth I technically difficult.
- *Gastroenterostomy* (loop of jejunum anastomosed to stomach) can be performed without partial gastrectomy. Indications include malignant duodenal invasion/stenosis (e.g. due to ➲ pancreatic cancer). The long afferent limb makes endoscopic access to the duodenal papilla at ERCP difficult (occasionally impossible) and may predispose to a range of complications (see ➲ afferent loop syndrome).

Complications of gastrectomy (see Fig. 2.4)

Peptic ulcer surgery has mortality of 0.3–1% (higher if emergency surgery required). Morbidity includes postoperative haemorrhage, leakage from anastomoses with abscess formation, ➔ post-gastrectomy syndrome, ➔ biliary reflux, and ➔ afferent loop syndrome (e.g. following Billroth II partial gastrectomy).

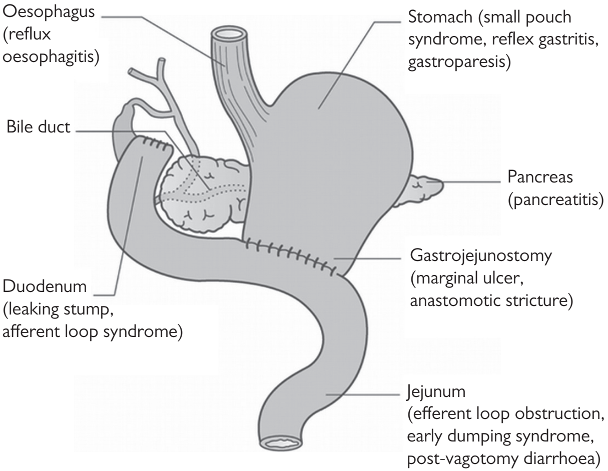
Oesophagus (reflux oesophagitis)
Stomach (small pouch syndrome, reflex gastritis, gastroparesis)
Bile duct
Pancreas (pancreatitis)
Gastrojejunostomy (marginal ulcer, anastomotic stricture)
Duodenum (leaking stump, afferent loop syndrome)
Jejunum (efferent loop obstruction, early dumping syndrome, post-vagotomy diarrhoea)

Fig. 2.4 Complications of partial gastrectomies.

Cholecystectomy

- 700,000 performed per annum in USA, mainly for ➔ gallstones.
- Laparoscopic cholecystectomy (LC) in >80% of cases, but conversion to open cholecystectomy (OC) needed in 5–10%. In patients with bile duct stones (➔ choledocholithiasis), duct clearance and sphincterotomy usually done by ▸ ERCP prior to surgery, but laparoscopic bile duct clearance increasingly performed during LC.
- Major complications: wound infection, bleeding, abscess formation, or bile leak (arising from cystic duct stump or damaged common bile duct (CBD)).
- Anatomical variants in biliary tree may be of high relevance to biliary surgeon, and lead to surgical complications. An accessory bile duct from right hepatic duct to cystic duct/gallbladder ('duct of Lushka') may result in biliary leak post-cholecystectomy. In 5%, right hepatic duct inserts low down into common hepatic duct, and may be mistaken for cystic duct. In 20%, cystic duct does not pass straight into common hepatic duct, but runs parallel to it, down towards papilla ('low inserting cystic duct'), with risk of incorrect ductal ligation at surgery and incorrect stent placement at ERCP.

- Gallbladders may be congenitally bilobed, double, intrahepatic, or absent.
- Bile duct injury occurs in 0.1–0.2% of OC and 0.5–1% of LC. Complications due to ➲ biliary strictures may develop immediately or up to 20y later.
- Mortality for cholecystectomy 0.2% overall (0.03% in <65y).

Roux-en-Y anastomosis

- Procedure involves dividing jejunum ~15 cm from ligament of Trietz, and mobilizing a loop of jejunum. Proximal limb anastomosed to appropriate anatomical site (Fig. 2.5). Divided end of jejunum anastomosed to jejunal loop along its course.
- Indications for Roux-en-Y anastomosis include ➢ biliary bypass procedure (e.g. hepatico-jejunostomy between jejunal loop and common hepatic duct), ➢ bariatric surgery, and as part of ➢ Whipple's procedure (pancreatico-duodenectomy).

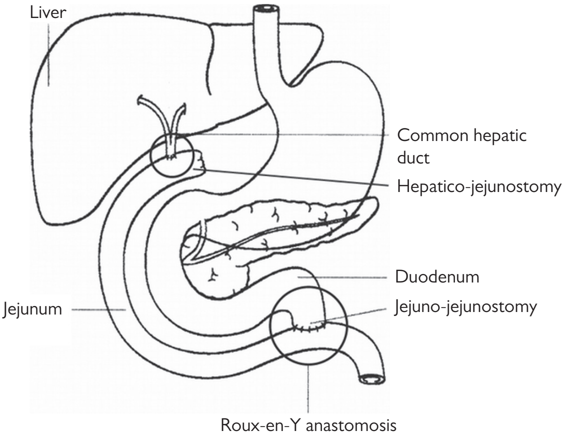

Fig. 2.5 Roux-en-Y anastomosis and hepatico-jejunostomy as part of ➢ biliary bypass procedure.

Biliary bypass procedures

Resection of extrahepatic bile duct, or biliary diversion, may be indicated for range of biliary problems, including:

- Iatrogenic/traumatic bile duct injury (e.g. post-➢ cholecystectomy) that is not amenable to endoscopic stent insertion.
- Biliary stone disease (e.g. ➲ Mirrizzi's syndrome).
- Persistent ➲ biliary stricture (e.g. secondary to ➲ pancreatic cancer or ➲ chronic pancreatitis).
- ➲ Choledochal cyst.

Operative approaches include:

- Whipple's resection (pancreatico-duodenectomy) (see ➢ 'Whipple's procedure', see below).
- Distal CBD, duodenum, and pancreatic head resection.
- Hepatico-jejunostomy: ➢ Roux-en-Y anastomosis, with jejunal loop onto common hepatic duct.
- Choledochoduodenostomy: usually side-to-side anastomosis of lower CBD onto duodenal bulb. Used for very distal strictures.
- Cholecystenterostomy: anastomosis of gallbladder onto small bowel—rarely performed.

❗ Practice point

In patients with hepatico-jejunostomy, subsequent ERCP to access the biliary tree usually impossible, due to Roux-en-Y anastomosis and long jejunal loop.

Whipple's procedure (pancreatico-duodenectomy)

Allen Oldfather Whipple (1881–1963) was an American surgeon, and medical historian on the Middle East after retirement. Also reported Whipple's triad in insulinoma (see ➲ pancreatic endocrine tumours), but did not describe ➲ Whipple's disease.

- Procedure involves excision of head of pancreas, gallbladder, distal CBD, duodenum, and distal stomach. Anastomoses result in gastrojejunostomy, choledochojejunostomy, and pancreatico-jejunostomy (Fig. 2.6).
- Indications include ➲ ampullary, duodenal, and ➲ pancreatic cancer (procedure possible in <20% of patients with pancreatic cancer, with subsequent 25% 5y survival), ➲ cholangiocarcinoma of distal bile duct, duodenal ➲ familial adenomatous polyposis, and occasionally ➲ chronic pancreatitis.
- Surgical morbidity >30% (e.g. biliary leak, pancreatic fistula, secondary haemorrhage, ➲ post-gastrectomy syndrome). Surgical mortality 3–5%.
- Pylorus-preserving pancreatico-duodenectomy (PPPD) has been advocated as an alternative to Whipple's procedure as means of ↓ early satiety and biliary reflux. Analysis to date suggests no significant differences in surgical morbidity/mortality or prognosis with ➲ pancreatic cancer after PPPD or standard Whipple's procedure.

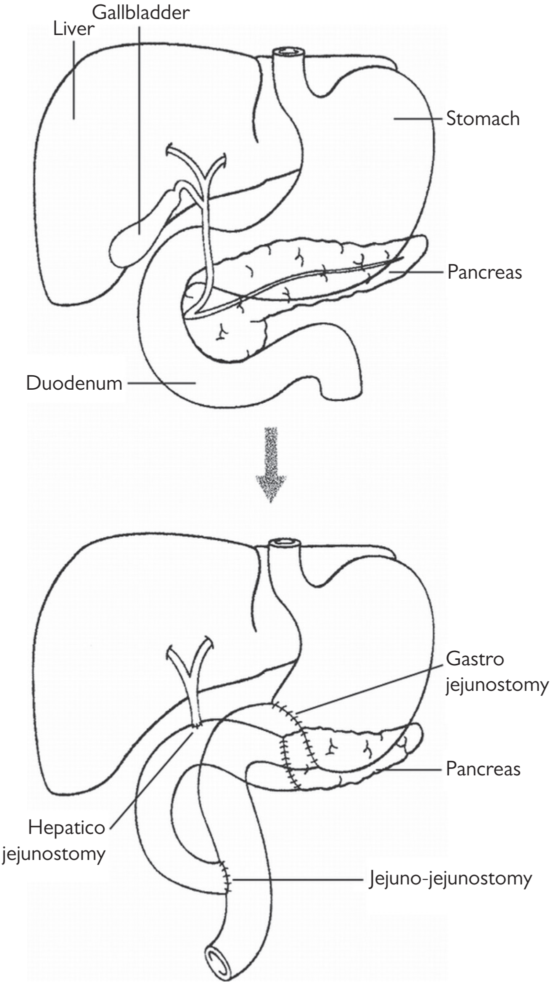
Gallbladder
Liver
Stomach
Pancreas
Duodenum
Gastro jejunostomy
Pancreas
Hepatico jejunostomy
Jejuno-jejunostomy

Fig. 2.6 Whipple's procedure (pancreatico-duodenectomy).

Ileostomy

Stoma constructed by bringing end or loop of ileum onto skin surface.

Indications

- Removal of colon because of ➔ Crohn's disease, ➔ ulcerative colitis, or ➔ familial adenomatous polyposis.
- Temporary or permanent faecal stream diversion because of colonic obstruction (e.g. ➔ colon cancer) or refractory ➔ Crohn's disease.
- Temporary ileostomies often made as 1st stage of surgical construction of ➢ ileoanal pouch (see p. 190).

Operations that expose ileal serosa to ileal effluent result in serositis. **Brooke ileostomy** (Fig. 2.7), developed in 1950s, involves everting mucosa and suturing to skin; this ileostomy is incontinent. '**Koch pouch**' variant features an ileal pouch, nipple valve, and ileal conduit leading to cutaneous stoma that can be flush to skin (Fig. 2.8).

Physiology of stoma function and their consequences.

- All ileostomies should discharge 300–800g of material/d, of which 90% is water. Small bowel is less good than colon at conserving sodium in conditions of low salt intake or high salt loss; patients with ileostomies have obligatory sodium losses of 30–40mEq/d. The increased water loss in stool contributes to relative oliguria and urolithiasis (≈5%, usually urate or calcium stones).
- **Resection of terminal ileum** (often necessary in ➔ Crohn's disease but not UC or FAP) can lead to ↓ bile acid reabsorption (secondary bile acids disappear from bile after ileostomy, but no important metabolic consequences recognized) and malabsorption of vitamin B_{12}.

Complications of ileostomy

- Fluid and electrolyte depletion with high output stoma.
- Herniation.
- Obstruction.
- Mechanical problems with poorly fitting stomal appliances cause skin excoriation or even fistula formation.

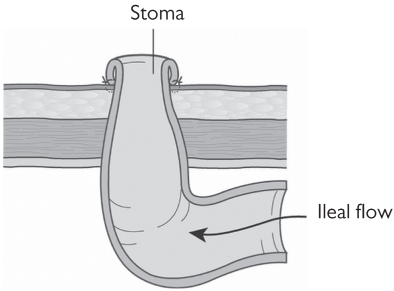

Fig. 2.7 Brooke ileostomy.

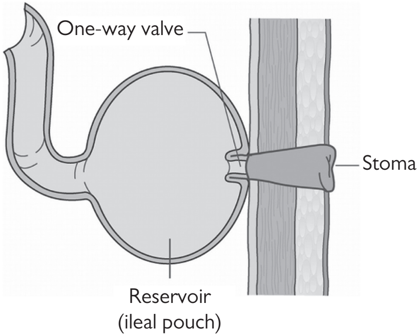

Fig. 2.8 Koch (continent) ileostomy.

Colectomy

- Removal of all or part of colon ± rectum. Resection of any part of large bowel entails mobilization and ligation of corresponding vascular supply.
- **Indications** include ➲ colonic or ➲ rectal cancer, ➲ diverticular disease, inflammatory bowel disease, caecal or colonic perforation, ▲ **bowel obstruction** ▲, bowel ischaemia or infarction, toxic ➲ megacolon, and prophylaxis in hereditary colon cancer syndromes.
- **Right and left hemicolectomies** remove ascending and descending colon respectively (extended hemicolectomy also involves resection of transverse colon). Isolated **transverse colectomy** uncommon. **Sigmoidectomy** may be accompanied by excision of all or part of rectum. Proximal and distal bowel anastomosed without absolute requirement for permanent stoma.
- **Proctocolectomy** Most frequently performed for ➲ ulcerative colitis or ➲ familial adenomatous polyposis. Involves resection of colon and rectum, followed by ileoanal anastomosis. In **panproctocolectomy**, the anus is also excised, resulting in permanent ileostomy.
- **Anterior resection** Used for cancers of proximal two-thirds of rectum. Involves resection of left-sided colon and part of rectum, with anastomosis to distal rectum. Usually accompanied by total mesorectal excision (dissection through avascular plane to remove connective tissue surrounding affected bowel). Patients will usually not require permanent colostomy, but may need temporary stoma. Anastomotic leak rate 3–11%, and in long-term impaired continence and sexual dysfunction are significant adverse effects.
- **Abdominoperineal resection** Principal indication is cancer of distal third of rectum, or recurrent or residual anal cancer. Involves removal of anus, rectum, and part of sigmoid colon, along with regional lymph nodes. Operative approach uses simultaneous incisions through abdomen and perineum. End of remaining sigmoid colon brought out to form permanent colostomy. Quality of life is generally worse than with low anterior resection.

- **Hartmann's procedure** Almost exclusively used for emergency surgery when immediate bowel anastomosis either not possible (including when viable but injured proximal bowel precludes safe anastomosis at time of initial operation), or for palliation of colorectal tumours. Perforation and obstruction common indications. Involves sigmoid colectomy with closure of rectal stump, and terminal colostomy. Perioperative mortality low, but at cost of colostomy that is never reversed in up to two-thirds of patients.

Colostomy

Stoma constructed by bringing end of colon onto abdominal wall.

Indications

- Partial removal of colon because of ➲ colon cancer, ➲ diverticular disease, or ➲ ulcerative colitis.
- Temporary faecal diversion post-surgery to allow bowel to be rested.
- Faecal incontinence not responsive to other treatments (see ▶ Approach to faecal incontinence).

Types of colostomy

- End. Created from one end of colon. Other end resected or oversewn (e.g. during ▹ Hartmann's procedure).
- Loop. Typically created during emergency procedures to create temporary stoma. Loop of bowel affixed to abdominal wall and two openings created for excretion of stool and mucus, respectively.
- Double-barrelled. Colon divided, and both ends brought out onto abdominal wall. Elimination occurs through proximal end. Usually temporary.

Complications of colostomy

- Herniation.
- Prolapse.
- Obstruction.
- High output.
- Skin excoriation.

Ileal pouch–anal anastomosis (IPAA)

Procedure of choice for patients requiring proctocolectomy for ➲ ulcerative colitis or ➲ familial adenomatous polyposis. Advantages:

- Removal of nearly all mucosal disease (in contrast to ileorectal anastomosis).
- Stoma not required.
- Anal sphincters not disturbed.

Although functional outcomes following pouch procedures are favourable, it remains technically demanding. The pouch must be constructed from ileum because direct anastomosis of ileum to anal verge results in excess stool frequency and anal seepage. There are several forms of pouch (Fig. 2.9): the J pouch is easiest to construct and has functional outcomes identical to those of more complex design.

Technical issues

Role of defunctioning ileostomy

Reported rates of pelvic sepsis vary from 0 to 25%, but are higher in patients undergoing a single-stage procedure. Indications for a temporary defunctioning ileostomy include steroids at the time of surgery, nutritional compromise, emergency surgery, and any concerns at operation about blood supply or anastomotic tension.

Stapled versus hand-sewn anastomosis

Debate arose because of opposing benefits of removing all colonic mucosa (implying a mucosal strip and technically demanding hand-sewn anastomosis) and preserving cuff of colonic mucosa to improve functional outcome. Randomized trial at Mayo Clinic found no difference in complication rate, but less night-time incontinence and better anal pressures in stapled group. Most surgeons now use stapled anastomosis.

Risk of cancer and dysplasia

Small risk of cancer in retained rectal mucosa, estimated at <1% 2y postoperatively. Risk higher if cancer or dysplasia in original colectomy specimen.

Clinical results

Average post-pouch stool frequency is six times daily and once at night. Incontinence more than twice per week occurs in 5% by day and 12% by night. Minor nocturnal incontinence occurs in up to 30% at 1y postoperatively. 30% need to wear pad to protect against seepage. Urgency experienced by 5% of patients at 1y, rising to 9% at 15y. Overall morbidity 25–30%. Failure is rare provided operation not done in error in patients with ➲ Crohn's disease. Most important factor is probably an experienced surgeon.

Complications and functional outcome

Complications are shown in Table 2.6. Complication rates can be significant and pouchitis remains a persistent and difficult problem.

- Great deal of variation in published clinical outcomes after pouch surgery. Latest data from UK Pouch Registry 🖱 https://www.acpgbi.org.uk/content/uploads/2016/07/Ileoanal-Pouch-Report-2017-FINAL.compressed.pdf show incidence of failure of <2%.
- One specific complication of IAPP is ↓ fecundity in young ♀, with 40–50% ↓ in pregnancy among those trying to conceive, probably as result of pelvic surgery and subsequent pelvic adhesions. Appropriate informed consent and exploration of alternative medical or surgical options should be undertaken.

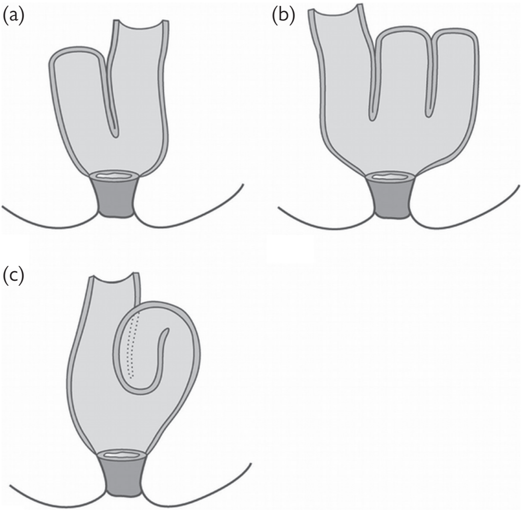

Fig. 2.9 Types of ileal pouch: a) J pouch; b) W pouch; c) S pouch.

Table 2.6 Complications of ileal pouch–anal anastomosis (IPAA)

Complication	Rate
Pelvic infection	5%
Abdominal sepsis	6%
Small bowel obstruction	17%
Peritonitis on closing ileostomy	4%
Anastomotic stricture	Very high: usually easy to dilate digitally
Impotence and retrograde ejaculation (men)	1.5% and 4%
Dyspareunia	7%

Section 3

Endoscopy

Patient preparation *194*
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Endoscopic retrograde cholangiopancreatography (ERCP) *210*
Colonoscopy *214*
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Patient preparation

Consent

Never forget that while invasive procedures may be routine for gastroenterologists, endoscopy can be a unique experience for patients, engendering fear and anxiety, as well as potential discomfort.

Consent is a *process* of discussion and decision-making, not an isolated event. The aim is to provide patients with sufficient clear information about proposed procedures to permit an informed choice as to whether or not to proceed. It should be seen as a partnership with the patient, not a matter of convincing or coercing them into accepting an intervention. *Acting without consent is battery*. See GMC guidance. 🖱 https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/consent.

Face-to-face discussion, information leaflets, and the consent form itself should address the following areas:

- The nature of the procedure, and the reason it is being proposed;
- Its benefits and likelihood of success;
- Risks and complications, including their incidence and severity;
- Alternatives, including those that are potentially more hazardous;
- Risks of not having the procedure.

Most health systems require that consent includes discussion of substantive risks of procedures that would influence a reasonable person making a choice. Every possible complication need not be discussed, but there is a prima facie right to be informed of small but well-established risks of non-trivial injury, and of any that would be of particular significance to the individual undergoing the procedure; an example is the 1 in 1,000 risk of perforation with colonoscopy. Complication rates are often derived from large multicentre studies, usually involving specialist centres. In future it is possible that consent forms will include rates specific to individual endoscopists or institutions.

Should a patient not want information, you should explain the potential consequences of not having it, particularly if this could invalidate consent. Document their refusal, and advise that they can change their mind at any time. You cannot withhold information at the request of another (e.g. a relative) unless you believe it might cause serious harm (more than simply becoming upset or refusing treatment). If you withhold information, this must be documented.

Valid consent requires the patient to have capacity: they must be able to understand and believe relevant information, reason the options, and communicate their choice. *There is a presumption of capacity until proven otherwise*. Decisions must be voluntary and free from external duress. Consent should only be obtained by a healthcare professional familiar with all aspects of the procedure; it is unlikely to be fully informed if the person taking consent is not fully informed!

Ideally consent should be obtained >24 hours beforehand; there must be time for patients to digest information and discuss further as necessary. For outpatients, information and consent forms may be sent to their home, allowing time to read thoroughly before signing.

In practice most units have a policy of consenting the patient immediately before the procedure: this needs to be done in a calm, unhurried manner with adequate privacy to discuss any issues and concerns. Decisions must be reviewed if significant time has passed, new information has become available, or the patient's condition has changed.

In emergencies, where immediate treatment is lifesaving and patients cannot consent (e.g. ↓ GCS), you may proceed under a 'defence of necessity', unless you are aware of an advance valid refusal.

Patients incapable of consenting

Policies differ between health systems. In England and Wales, consent cannot be given or withheld on behalf of mentally impaired patients (e.g. by next of kin), unless they have medical power of attorney. Nevertheless, it is good practice to discuss procedures with relatives beforehand. A consent form specific to those unable to give consent is signed by a senior doctor looking after the patient and the endoscopist.

Capacity is not absolute but varies according to patient understanding and complexity of the procedure, and can fluctuate with time. You should attempt to maximize patient autonomy, which may include involving patient advocates. For full guidance, see the Mental Capacity Act 2005 (England), or Adults with Incapacity Act 2000 (Scotland).

Minors

In general, parents/guardians provide consent for children up to age 16. Children <16y may consent for a procedure if they sufficiently understand the whole process, even if parents refuse. However, they cannot override parental consent for procedures the latter have accepted.

In the very unusual event of parental refusal to consent for a child (without capacity) in a situation where refusal may have serious consequences for the child, legal recourse may be necessary. Involve senior hospital management and the legal department. Going to court to treat a child against parental wishes is extremely unpleasant, and may often be avoidable if parental fears (justified or not) are addressed early.

Withholding/withdrawal of consent

Withholding consent is straightforward. A patient who is competent to make an informed decision can refuse consent to any procedure, even if this may lead to their death. It is important to record the refusal and discussion of its implications. For patients lacking capacity, a valid *advance directive* refusing a specific intervention is legally binding.

Withdrawal of consent during a procedure may be more complicated. Even with sedation, patients may struggle (nevertheless the amnesic effect of the drug may result in them having no recall afterwards). If the endoscopist is nearing completion they may be inclined to continue for a couple more minutes, but ultimately a clear demonstration by the patient they wish the procedure to stop should result in its abandonment.

Bowel preparation

Bad bowel preparation is the bane of colonoscopy. Some sort of bowel preparation is almost always needed. For examination of the left colon, a phosphate enema should be given, either at home on the morning of the procedure or failing that 15–60min pre-procedure in the endoscopy unit. In patients with diverticular disease or strictures, full bowel preparation may be needed. Frail, ill, and elderly patients may need inpatient preparation.

- **Modification to diet and medication** Iron should be stopped 1wk beforehand. Constipating agents should be avoided for 24h pre-procedure. Colon cleansing is aided by liquid diet for 24h prior to examination.
- **Purgative regimens** (editor's note: remember the difference between regimen and regime; the latter is a term reserved for authoritarian dictatorships): see Table 3.1 and Box 3.1.

Sedation

- Degrees of sedation used for endoscopy are: no sedation, conscious sedation, deep sedation, and general anaesthesia.
- Diagnostic upper GI endoscopy may be well tolerated with local anaesthetic throat spray only (e.g. lidocaine 2%), but conscious sedation (patient able to make purposeful responses to verbal/tactile stimuli, with spontaneous ventilation) used for most endoscopies. Combination of throat spray and IV sedation should be used with caution, in view of possible ↑ risk of aspiration.
- Following required in patients undergoing conscious sedation:
  - Supplemental oxygen via nasal cannulae (e.g. 2L/min).
  - IV access throughout procedure.
  - Pulse oximetry (but demonstrates only hypoxaemia, and not hypoventilation, so clinical assessment remains vital).
  - Cardiac monitoring.
- **Choice of agent and doses** Conscious sedation usually involves use of a **benzodiazepine** (e.g. IV midazolam 1–5mg) and an **opiate** (e.g. IV pethidine 25–50mg, fentanyl 20–100μg; fentanyl increasingly used as less emetogenic than pethidine), administered by the endoscopist. An opiate should be given first, because of slower rate of action, and careful titration of drug dosages to patient response essential. In some countries, and for complex procedures (e.g. ERCP), anaesthetist-administered deep sedation with propofol (rapid action and recovery, but narrow therapeutic window) is increasingly used.
- In general, use lowest possible dose: e.g. 1–2mg midazolam for diagnostic upper GI endoscopy (if sedation needed) and 2–3mg midazolam with 50μg fentanyl (or 25mg pethidine) for colonoscopy. ERCP may require higher doses.
- There is increasing use of inhaled nitrous oxide (e.g. Entonox®) since this gives sedation which wears off very quickly.

Table 3.1 Bowel cleansing regimens for colonoscopy

Preparation	Advantages	Disadvantages	Notes
Magnesium salts: have strong purgative and osmotic effects	Magnesium citrate has milder flavour than magnesium sulfate	Need to drink 2L of fluid	Widely used in UK. Effective when combined with oral senna
Polyethylene glycol-based solutions (e.g. Klean-Prep®)	Safe, effective	Large volume (4L) often difficult for patients to manage	Widely used in UK
Non-absorbable carbohydrates (mannitol, lactulose sorbitol) act as osmotic laxatives	Avoids cramping effects of purgatives	Sweet and unpalatable in the large volume required	Not recommended. Hydrogen produced by fermentation results in risk of explosion during electrosurgical procedures
Low volume sodium phosphate	Well tolerated. 2 x 45ml aliquots of sodium phosphate taken orally the evening before and 4h prior to colonoscopy produce vigorous catharsis	Fluid balance shifts or hyperphosphataemia can be significant, especially in the presence of cardiac or renal disease	

Box 3.1 General advice given to patients on preparing for colonoscopy

- Stop iron tablets 7d before exam.
- Continue all other medications and laxatives until procedure.
- Follow low-residue diet for 1–2d before examination (no cereals, nuts, or muesli).
- No solid food after lunch on day preceding colonoscopy, but plenty of clear fluids to avoid dehydration.
- After exam, better not to use public transport, but if essential patient MUST be accompanied.
- No alcohol or operation of heavy machinery for 24h after procedure.
- No driving or signing legal documents on day of procedure if sedation given.

Management of hypoxaemia/hypoventilation

- Sedation implicated in >50% of endoscopic complications (p. 204), including aspiration, oversedation, hypoventilation, and airway obstruction. Risks crudely correlate with pre-procedure American Society of Anesthesiologists (ASA) score (Box 3.2). Involvement of senior endoscopist and anaesthetist essential in patients with ASA >3.
- Management includes protection of airway (e.g. 'jaw thrust'), administration of reversal agent (flumazenil 250–500μg IV for benzodiazepines, naloxone 400μg IV/IM for opiates), continued supplemental oxygen (via mask), and emergency mechanical ventilation as necessary. Jaw thrust and flumazenil sufficient in most cases, and addition of naloxone rarely needed when combination of benzodiazepine and opiate has been used.
- General anaesthesia for endoscopy generally reserved for situations where cooperation difficult (e.g. children), or where airway protection with endotracheal tube important (see comments on variceal bleeding in ▲ **acute upper GI bleeding** ▲).

Box 3.2 American Society of Anesthesiologists (ASA) status

1 No organic, physiological, biochemical, or psychiatric disturbance. Condition for which procedure to be performed localized, with no systemic disturbance.
2 Mild to moderate systemic disturbance caused by either condition to be treated or other pathological processes.
3 Severe systemic disturbance or disease from whatever cause, even though may not be possible to define degree of disability with certainty.
4 Severe systemic disorders that are already life-threatening and not always correctable by intervention.
5 Moribund patient who has little chance of survival but submitted to intervention/operation in desperation.

Antibiotic prophylaxis

Bacteraemia following endoscopy is not uncommon, but complications are infrequent and endocarditis extremely rare. Very little evidence antibiotic prophylaxis efficacious,[1] but risk of bacteraemia highest for endoscopic dilatation, variceal sclerotherapy (less for band ligation), ERCP, and colonoscopy (Box 3.3). See BSG guidelines (2009). 🖱 https://www.bsg.org.uk/resource/bsg-guidelines-on-antibiotic-prophylaxis-in-gastrointestinal-endoscopy.html.

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[1] ASGE Standards of Practice Committee *et al*. (2015). *Gastrointest Endosc* **81**: 81–9.

- Prophylaxis no longer recommended for patients with cardiac valve disease or replacement, pulmonary-systemic shunts, or vascular grafts in view of absence of evidence for efficacy and potential risks of adverse events. However, diagnosis of endocarditis should be considered in patients presenting with symptoms or signs of infection in the weeks following procedure.
- Patients with ➲ cholangitis or ➲ variceal bleeding should be established on antibiotic therapy irrespective of endoscopy.
- ERCP does not require routine antibiotic prophylaxis, but should be given in setting of ➲ pancreatic pseudocysts, immunosuppression, hilar ➲ cholangiocarcinoma, ➲ primary sclerosing cholangitis, and in any situation of predicted or proven incomplete drainage at ERCP. It should be given when performing cholangioscopy.

Box 3.3 Recommendations for antibiotic prophylaxis

- ERCP with anticipated incomplete drainage of biliary tree (e.g. primary sclerosing cholangitis, hilar cholangiocarcinoma), or for communicating pancreatic cyst or pseudocyst: → CIPROFLOXACIN 500mg PO 1h before (avoid in children), or → GENTAMICIN 1.5mg/kg IV over 2–3min.
- ERCP for biliary complications following liver transplant: One of → CIPROFLOXACIN or → GENTAMICIN as above, plus one of → AMOXICILLIN 1g IV or → VANCOMYCIN 20mg/kg IV over 1h.
- EUS with FNA for cystic lesions in or near pancreas: → CO-AMOXICLAV 1.2g IV or → CIPROFLOXACIN. No prophylaxis indicated for solid lesions.
- Patients with profound immunocompromise (e.g. severe neutropaenia <0.5 × 10^9 cells/L, advanced haematological malignancy) undergoing high-risk procedures (dilatation, variceal sclerotherapy, laser therapy, or colonoscopy). Discuss with haematology and microbiology.
- PEG/PEJ insertion: single dose → CO-AMOXICLAV IV or → CEFUROXIME 750mg IV ↓ peristomal wound infection. → TEICOPLANIN 400mg IV if penicillin allergic.

Antiplatelet therapy and anticoagulation

Need to withhold or reverse antiplatelet therapy or anticoagulation depends on clinical condition of patient, underlying indication for such medication (thrombotic risk), and nature of endoscopic procedure (bleeding risk). See BSG guidelines on endoscopy in patients on antiplatelet or anticoagulant therapy (2016). 🖱 https://www.bsg.org.uk/resource/bsg_esge_anticoag_16.html. The following general principles apply:

- Procedures stratified as those with low (Box 3.4) or high (Box 3.5) bleeding risk. Within these categories, patients then considered as to whether their risk of thrombosis would be low or high should antiplatelet or anticoagulant drugs be discontinued.

- **Acute GI haemorrhage** Immediate risk to patient may outweigh risk of thrombosis. Patients need to be assessed on individual basis. Heparin may be substituted for warfarin if patient considered high risk of thrombosis. Clopidogrel should not be discontinued in patients with coronary stents without cardiology input, and if so limited to a maximum of 7d. Aim should be for urgent endoscopy as soon as patient clinically stable: haemostasis may allow no cessation of therapy. For guidance should immediate emergency reversal of antiplatelet or anticoagulant drugs be required, see Box 3.6.

Antiplatelet drugs

- **Aspirin** may be continued for all endoscopic procedures.
- **P2Y12 receptor antagonists** (clopidogrel, prasugrel, ticagrelor) may be continued for low risk procedures.
- For other antiplatelet drugs (e.g. dipyridamole, ticlopidine, abciximab), insufficient evidence exists to provide robust guidance, but for procedures with high bleeding risk, temporary discontinuation and aspirin monotherapy may be desirable.

Anticoagulants

- **Warfarin** should generally be continued for procedures with low bleeding risk, so long as INR within therapeutic range. If supratherapeutic, generally appropriate to ↓ dose until INR within range.
- **Direct acting oral anticoagulants (DOACs)**. Currently rivaroxaban, dabigatran, apixaban, and edoxaban licensed in UK. Rapid onset and offset kinetics favourable, but associated with higher risk of bleeding so duration of temporary withholding differs between procedures with low and high risk of bleeding. No high-risk thrombosis category for these drugs as not indicated for prosthetic heart valves.
- When considering risk stratification, patient preference should be considered, as thrombotic event such as stroke may be completely unacceptable to some, even if risk very low.

Box 3.4 Low-risk procedures

- Diagnostic procedures ± biopsy.
- Biliary or pancreatic stenting.
- Diagnostic EUS.
- Device-assisted enteroscopy.

Drug management in these patients:

- **Aspirin**: Continue.
- **P2Y12 receptor antagonists**: Continue.
- **Warfarin**: Continue if INR in therapeutic range.
- **DOACs.** Omit morning dose on day of procedure.

Box 3.5 High-risk procedures

- Variceal therapy.
- Polypectomy.
- ERCP with sphincterotomy.
- EUS with FNA.
- PEG.
- Stricture dilatation.
- Oesophageal, enteral, or colonic stenting.
- Ampullectomy.
- Endoscopic mucosal resection or submucosal dissection.

Drug management in these patients:

- **Aspirin**: Continue.
- **P2Y12 receptor antagonists**:
  - *Low thrombotic risk conditions* (ischaemic heart disease without coronary stenting, cerebrovascular disease, peripheral vascular disease): Stop 5d before endoscopy.
  - *High thrombotic risk conditions* (coronary artery stents): Liaise with cardiologist, but consider stopping for 5d before endoscopy if >12mo after insertion of drug-eluting stent, or >1mo after bare metal stent.
- **Warfarin**:
  - *Low thrombotic risk conditions* (prosthetic aortic valve, xenograft heart valve, AF without valvular disease, >3mo after venous thromboembolism). Stop warfarin 5d before endoscopy, check INR prior to procedure to ensure <1.5, restart warfarin on evening after procedure and check INR 1wk later to ensure re-anticoagulated.
  - *High thrombotic risk conditions* (prosthetic heart valve in mitral position or with AF, AF + mitral stenosis, <3mo after venous thromboembolism). Stop warfarin 5d before endoscopy and start LMWH 2d after stopping warfarin. Give last dose of LMWH ≥24h before procedure, restart warfarin on evening of procedure but continue LMWH until INR therapeutic.
  - *Thrombophilia syndromes*. Discuss with haematologist.
  - Note: There is 10–15% risk of major bleed post-biliary sphincterotomy with warfarin restarted within 3d.
- **DOACs.** Stop drug ≥48h before procedure (72h for dabigatran if eGFR<50ml/min.

Box 3.6 Rapid reversal of antiplatelets and anticoagulation

- **Antiplatelets** In rare circumstances where immediate reversal mandated, discuss with Haematology, but 1–2 pools platelets likely required.
- **Warfarin** (and other coumarins). If acute bleeding and require immediate reversal, use prothrombin complex concentrate + vitamin K 0.5–1mg IV. If bleeding stopped, consider vitamin K based on balance of thrombosis risk compared to further haemorrhage. If discontinuing warfarin indefinitely, give vitamin K 10mg IV.
- **DOACs** Some evidence prothrombin complex concentrate reverses rivaroxaban (but not dabigatran or apixaban). Monoclonal antibody (idarucizumab) that reverses dabigatran, and decoy receptor (andexanet alfa) that reverses rivaroxaban, apixaban, and edoxaban, developed. Limited availability and experience, so discuss with Haematology if may be required.

Sample preparation for histopathology

For **routine histology**, immerse biopsies in at least 10x biopsy volume of formaldehyde-based fixative before drying occurs. Preparation for **electron microscopy** ideally requires fixation in glutaraldehyde. **Enzyme assays and some antibody staining** require snap freezing in liquid nitrogen. Single biopsies can be put straight into formalin or mounted on piece of card, but for biopsy series (e.g. from Barrett's mucosa or colonoscopy) better to place biopsies on straight line on thin strip of nitrocellulose. This can then be aligned on its side in a paraffin block ready for sectioning, which produces strip of biopsies together on 1 slide in known order: check with your pathology department as to local preferences. Terminal ileal biopsies should be included with colonic biopsies, but preferable to send oesophageal, gastric, and duodenal biopsies in separate specimen pots, as metaplasia at these sites can cause confusion as to site of origin of individual biopsies.

How many biopsies?

The more tissue sent, the more likely an accurate diagnosis. In most cases, several (e.g. 4) biopsies from a single site of macroscopic pathology (e.g. colonic tumour) suffices. Where more diffuse pathology suspected (e.g. inflammatory bowel disease), more biopsies may be needed to make correct diagnosis and establish disease extent. Ideally biopsies from normal as well as inflamed areas should be included, with their anatomical order. Including endoscopy report very helpful for histopathologist. Guidelines suggest number and site of biopsies for some conditions:

- **Gastritis**: 5 biopsies—2 antral, 2 body, and 1 incisura.[2]
- **Barrett's oesophagus**: quadrantic biopsies at 2cm intervals within Barrett's segment.[3]
- **Coeliac disease**: 4 biopsies from D2, 2 from D1.

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[2] Dixon MF *et al*. (1996). *Am J Surg Pathol* **20**: 1161–81.

[3] Fitzgerald RC *et al*. (2014). *Gut* **63**: 7–42.

Decontamination and disinfection of endoscopes

Range of infections have been transmitted during endoscopy, including bacteria (➔ Salmonella, ➔ Pseudomonas), and viruses (➔ hepatitis B & C). Theoretical risk of transmission of prion disease (Creutzfeldt–Jakob disease) necessitates careful consideration of merits of endoscopy in patients with any possibility of having these diseases (Box 3.7), as conventional sterilization ineffective, and long-term quarantine or destruction of endoscopes required if used. Multistep process involved in cleaning and sterilizing endoscope after use. Detailed recommendations can be found in the report 🖱 https://www.bsg.org.uk/resource/guidance-on-decontamination-of-equipment-for-gastrointestinal-endoscopy-2017-edition.html of BSG Endoscopy Committee working party on cleaning and disinfection of endoscopes.

- Manual cleaning during lists and between patients essential. Blood/mucus/debris wiped off after use; suction and accessory channels washed through with dilute detergent, and brushed with single-use devices.
- Use of automated endoscopic reprocessors mandatory. Cycles of disinfection, washing, and drying, usually performed over 30min in automated washing system. Units recommended to move away from aldehyde-based disinfectants due to fixative properties.
- Keep records of endoscope and accessories used for each patient.
- Endoscopy should be avoided where possible in patients with suspected or confirmed vCJD.
- Single-use accessories used wherever possible.
- Out-of-hours endoscopy should only be done where assistant available with specialist knowledge of endoscopes and decontamination.
- Given universal precautions for endoscope decontamination, little logic in placing high-risk patients at end of procedure lists, with exception of patients with atypical mycobacterial chest infections.
- Use of purpose-built drying and storage chambers may obviate need for full reprocessing cycle prior to each endoscopy list.

Advice on endoscopy in patients at risk of vCJD

This is covered in guidelines 🖱 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/530418/HTM0106_PartA.pdf from the UK Department of Health.

Box 3.7 Staff admitting patients for endoscopy should ask all patients

'Have you ever been notified that you are at increased risk of CJD/vCJD for public health purposes?'

If answer is yes, appropriate precautions as per the consensus guidelines should be taken. In essence, admitting staff need to scan case notes for any evidence of undiagnosed neurological illness; in such circumstances, advice needs to be obtained from a neurologist before elective endoscopy, and/or the procedure should be rescheduled.

Selection of disinfectant

Ideal agent will be effective against pathogens (including spores, *M. tuberculosis*, and blood-borne viruses), compatible with instruments and washers, non-irritant, and affordable. Glutaraldehyde is widely used, but all aldehydes can be irritant and sensitizers, which may limit long-term utility. Peracetic acid and chlorine dioxide are both effective.

Upper GI endoscopy

Development >50y ago of flexible endoscopes revolutionized diagnostics, and subsequently therapy, in GI disease. Working length of modern gastroscopes ~110cm, with external diameter of 5–12.5mm. Most usually inserted perorally, but fine tube may be inserted transnasally.

Oesophagogastroduodenoscopy (OGD)

Indications

- Diagnostic:
  - Evaluation of upper GI symptoms (e.g. reflux, dysphagia).
  - Investigation of iron-deficiency anaemia or bleeding.
  - Tissue sampling (e.g. in suspected ➲ coeliac disease).
  - Surveillance (e.g. ➲ Barrett's oesophagus).
- Therapeutic:
  - Haemostasis (e.g. ▲ **upper GI bleed** ▲).
  - Dilatation and stent insertion.
  - Tumour ablation.
  - ➢ Percutaneous endoscopic gastrostomy.

Contraindications

Most are relative, depending on clinical scenario:

- Haemodynamic instability.
- Recent myocardial infarction.
- Acute abdomen.
- Severe coagulopathy.

Complications

Endoscopy is an invasive procedure, carrying definite risks (see also ➢ 'sedation', p. 196).

- Cardiorespiratory adverse events (aspiration pneumonia, hypoventilation, vasovagal attack, arrhythmias) account for >50% of complications. Risk correlates with age and comorbidity.
- Respiratory depression is a particular risk with combination of sedative benzodiazepines and opiate analgesics.
- Risk in individual patient relates to:
  - Patient factors (age, comorbidity, anaesthetic risks).
  - GI disease-related factors (large polyp, malignant stricture).
  - Endoscopic technique (e.g. endoscopist experience, inherent risk of specific intervention).

Diagnostic upper GI endoscopy very low risk (morbidity 0.1%, mortality ~0.01%). Perforations in 0.01%, usually due to (unsuspected) anatomical abnormality such as pharyngeal pouch or oesophageal stricture. Certain therapeutic procedures (oesophageal dilatation, percutaneous endoscopic gastrostomy (PEG) insertion, variceal therapy) associated with specific risks.

Percutaneous endoscopic gastrostomy (PEG)

Gastrostomy feeding is the most common method of nutritional support in patients requiring tube feeding for >4wk (up to which time ➢ nasogastric tube more appropriate). Gastrostomy tubes can be placed endoscopically (PEG), radiologically (RIG), or (rarely) surgically.

Indications

- PEG insertion increasingly performed when enteral feeding required for >4wk (10% of nursing home residents in USA have had PEG).
- Main indications include neuromuscular disease (e.g. stroke, motor neuron disease, dementia) and oropharyngeal cancer.
- Ongoing debate surrounds maintenance of enteral feeding in patients with end-stage progressive disease, but PEG tubes certainly better tolerated than long-term nasogastric feeding.

Contraindications

- Inability to bring anterior gastric wall in apposition to anterior abdominal wall (e.g. subtotal gastrectomy, ascites, severe obesity).
- GI tract obstruction.
- Malignant gastric/peritoneal infiltration.
- Gastric varices.
- Uncorrectable coagulopathy.

Technique

- 'Pull technique' entails:
  - Endoscopy to exclude any lesions within upper GI tract.
  - Endoscopic localization of anterior gastric wall, with corresponding point on anterior abdominal wall identified using transillumination and finger indentation.
  - Sterilization of skin, local anaesthetic infiltration (e.g. lidocaine 2% 4ml), and 5mm incision into skin at site of planned insertion.
  - Insertion of trocar, followed by looped string, percutaneously into stomach under endoscopic vision.
  - String grabbed endoscopically with endoscopic snare, and drawn retrogradely out of mouth on removal of endoscope. A 9–16F feeding tube is attached to string and drawn into position by traction at the skin (Fig. 3.1).
  - Button of PEG tube keeps it lightly impacted against gastric wall.
- Pre-procedure antibiotics (e.g. co-amoxiclav 1.2g IV) ↓ risk of peristomal infection.
- PEG can be modified with addition of jejunal feeding tube, which may ↓ risk of reflux and gastric aspiration in patients with delayed gastric emptying.

Complications

- Major complications in 3%, minor complications in 20%:
  - Infection: cellulitis, peritoneal, or abdominal wall abscess, necrotizing fasciitis, local peritonitis.
  - Haemorrhage. Localized vessel damage may respond to tamponade by tightening intragastric flange against skin (e.g. moving skin clasp at skin surface from 4cm to 3cm). If persistent/life-threatening bleeding, consider interventional angiography or surgery.

  - Bowel perforation. Usually involves catheter passing through anteriorly situated transverse colon. Emergency laparotomy if peritonitic; otherwise discontinue PEG use and give broad-spectrum antibiotics for 4wk, at which time remove tube endoscopically.
  - Tube occlusion. May be reopened by vigorous flushing with warm water (consider prior installation of pancreatic enzymes in bicarbonate, or manual recanalization with brush or balloon catheter. Avoid wires).
  - Tube displacement. Replace catheter within 5d to maintain nutrition. If dislodged within 1mo of original placement, relocate endoscopically. However, mature tracts easily recannulated: maintain patency by placing Foley catheter within 6–12h (may be successful up to 5d, and can perform under screening if in doubt). Definitive tube replacement can then be performed under endoscopic or radiologic guidance.
  - Leakage. Due to excessive tube motion or overtight fixation. Exclude partial obstruction.
  - Buried bumper syndrome (in which gastric mucosa grows over inner bumper of PEG, making it difficult to remove). Thought to arise due to excessive tension between inner and outer bolsters. Presents as mechanical failure to deliver feed associated with abdominal pain. Endoscopic examination confirms blockage, and may allow bumper release. All symptomatic patients should have tube replaced. Prevent by rotating tube every few days following placement and releasing tube traction at 10d once tract formed.
- Procedure-related mortality 0.5–2%, and overall 30d all-cause mortality 10–15% (largely reflecting underlying disease, but emphasizes need to be sure patient not put through futile unnecessary intervention in last few days of life).
- Pneumoperitoneum in 20%, but rarely of significance.

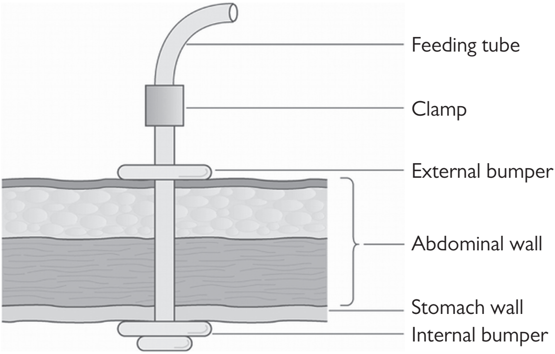

Fig. 3.1 Percutaneous endoscopic gastrostomy tube.

Radiologically inserted gastrostomy (RIG)

Alternatives to PEG include radiologically inserted gastrostomy (RIG) or surgical approaches. May be considered in patients undergoing planned curative surgery for oropharyngeal cancer, as rare incidences of metastases at gastrostomy site due to endoscopic insertion reported (possibly due to pulling the tube past tumour, a step absent during RIG insertion). RIG insertion involves:

- Distension of stomach with air via NG tube. This extends stomach below costal margin and liver and displaces transverse colon from epigastrium, thereby facilitating safe gastric puncture.
- Some techniques include gastropexy (fixation of stomach to anterior abdominal wall) using anchor sutures.
- Gastric puncture and insertion of guidewire once intragastric position confirmed by aspiration of air into syringe and/or injection of contrast, outlining gastric rugal folds.
- Dilation of tract to requisite size.
- Gastrostomy tube inserted (either using intragastric balloon for retention or pigtail tube).

Technical success of RIG placement approaches 100% and often successful when attempts at PEG placement fail. Main reason for RIG failure is stomach positioned in chest, which precludes puncture. Rates of complications similar to those for PEG placement. However, deep stomal infections are rare and prophylactic antibiotics not routine practice as tube not pulled through flora of oropharynx.

Enteroscopy

Two endoscopic methods of imaging the 5m of small intestine currently available:

- **Push enteroscopy** Useful for examining upper small intestine, but limited to proximal 50–75cm of jejunum. Biopsy and therapy possible through standard size operating channel. Technique carried out using dedicated 240cm enteroscope (or paediatric colonoscope that approximates in length and handling characteristics).
- **Video capsule endoscopy** (VCE; 'wireless enteroscopy') has been significant advance, providing possibility of visualizing areas of bowel inaccessible to conventional flexible endoscopy (i.e. most of small bowel). The 11x26mm capsule is swallowed, and video images transmitted to data recorder worn on patient belt for ~8h.

Indications

- Unexplained GI tract bleeding/iron-deficiency anaemia, following negative upper and lower GI tract endoscopies.
- Symptoms or inflammatory markers suggestive of Crohn's disease, but negative imaging/endoscopies.
- Investigation of refractory coeliac disease to look for coeliac-associated complications.
- Potential small bowel pathology (e.g. ➲ Whipple's disease, ➲ Peutz–Jeghers, intestinal ➲ parasite, ➲ NSAID enteropathy).

Contraindication

- Intestinal stricturing.
- Altered intestinal anatomy (e.g. Roux-en-Y enterostomy)

Complications

- Enteroscopy: similar to ➢ oesophagoduodenoscopy.
- Capsule endoscopy:
  - Capsule retention due to strictures or diverticula in 1–2%. Patients with abdominal pain should have imaging to exclude stricture before VCE. All patients should be counselled on risks of capsule retention.
  - Risk of retention (which may require laparotomy) ↓ by prior ingestion of **patency capsule**, comprising lactose shell which dissolves quickly and completely once inside GI tract. Capsule has two timer plugs on both sides, designed to resorb over 12h. Excretion of patency capsule can be confirmed by X-ray or through handheld scanner that will detect emitted electromagnetic signal. If patency capsule excreted within 30h of ingestion, or if excreted intact, the patient can safely undergo VCE.
  - Plain AXR should be taken if video analysis fails to show capsule has entered colon. Patients should not undergo MRI after VCE until they have passed capsule.

Comparative role of capsule endoscopy

- **VCE vs. endoscopy**: diagnostic yield of capsule endoscopy superior to push enteroscopy for defining obscure small bowel bleeding in those with negative endoscopy and colonoscopy.
- **VCE vs. small bowel radiology:** VCE superior to barium radiology in identifying active small bowel Crohn's disease. However, radiological imaging essential in identifying strictures, which may preclude the use of CE.[4]

Double-balloon (push and pull) enteroscopy (DBE)

- The DBE system consists of a video endoscope with a diameter of 8.5mm and working length of 200cm, and flexible overtube 145cm long and outer diameter of 12mm. Air used to inflate and deflate latex balloons attached to distal end of enteroscope.
- Inflated balloon on overtube used to maintain stable position while enteroscope advanced. Overtube balloon then deflated while enteroscope balloon inflated and overtube advanced along distal end of enteroscope. This 'push' procedure is followed by 'pull' procedure, when both enteroscope and overtube pulled back with both balloons inflated. Can be repeated several times to allow visualization of entire small bowel. Average time for procedure: 75min.
- Anterograde DBE superior to push enteroscopy in length of insertion. Diagnostic yield of DBE is 43–85%. DBE has also been used to remove retained video capsules, avoiding need for surgery.

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[4] Sidhu R *et al*. (2008). *Gut* **57**: 125–36.

Endoscopic retrograde cholangiopancreatography (ERCP)

Technique

Side-viewing duodenoscope allows selective cannulation of biliary system, and insertion of cannulae into pancreatic/common bile ducts, with ductal system delineated by contrast injection and X-ray imaging.

Indications

No role for ERCP as primarily diagnostic technique because of risks of procedure and availability of less invasive modalities to investigate pancreaticobiliary system (MRI/MRCP, CT, transabdominal and endoscopic US). Indications include relief of biliary obstruction with endoscopic stenting (e.g. for ➔ pancreatic cancer, ➔ cholangiocarcinoma), removal of stones from common bile duct, and biopsy or cytological brushing of biliary strictures/lesions.

Contraindications

Most relative, and depend on clinical scenario.

- Altered surgical anatomy (e.g. Roux-en-Y anastomosis) may make endoscopic access difficult/impossible.
- Coagulopathy: aim for INR 1.3, platelets >60 × 10^9/L, and patient off antiplatelets other than aspirin (if possible) and anticoagulation if sphincterotomy expected.

Complications (Table 3.2)

Higher in units performing <200 ERCPs/y, and with endoscopists performing <40 ERCPs/y, but 'patient-related' factors probably even more important. Overall complication rate 5–25%, depending on patient population.

- **Pancreatitis** is most common complication of ERCP (3–5% in straightforward cases). Severe course in 30%, with mortality rate from sphincterotomy-induced pancreatitis = 0.5%. Several risk factors associated with post-ERCP ➔ acute pancreatitis (Box 3.8). Careful patient selection vital, as ERCP most dangerous for people who need it least (20–30% risk of pancreatitis in young ♀ with abdominal pain, normal bilirubin, and non-dilated bile duct). Single dose of rectal NSAID given before or immediately after ERCP ↓ rates of pancreatitis, and is now used.
- **Retroperitoneal perforation** occurs in <1% of sphincterotomies. May present acutely with surgical emphysema, but pain in absence of rise in serum amylase may also provide diagnostic clue. CT scanning usually required. Most settle with IV antibiotics and strict NBM, but close observation required in view of risk of retroperitoneal sepsis and abscess formation, which may require percutaneous or surgical drainage.

- **Bleeding** relating to sphincterotomy usually settles spontaneously, but ➢ endoscopic haemostasis techniques may be needed.
- **Cholangitis** in ~2% of patients following ERCP, usually when intrahepatic ducts have been filled with contrast but effective biliary drainage not obtained. Managed with broad-spectrum IV antibiotics, and further efforts to establish effective drainage (e.g. percutaneous transhepatic drain (PTD)).

Table 3.2 ERCP complications and severity grading

	Mild	Moderate	Severe
Bleeding	Clinical evidence of bleeding, but ↓ in Hb <30g/L, and no transfusion required	Transfusion required, but <5U, and no angiographic or surgical intervention	>4U transfused, or angiographic/surgical intervention
Perforation	Possible, or only very slight leak, with <4d treatment required	Proven perforation treated medically for 4–10d	Medical treatment for >10d, or intervention (percutaneous or surgical)
Pancreatitis	Amylase >3xULN >24h after ERCP, with hospital stay extended by 2–3d	Hospitalization for 4–10d	Hospitalization >10d, haemorrhagic pancreatitis, phlegmon, pseudocyst, or intervention
Cholangitis	Temp >38°C for 24–48h	Septic illness requiring >3d hospital treatment, or endoscopic/radiographic intervention	Septic shock or need for surgery

Reproduced with permission from Cotton PB *et al.* (1991) *Gastrointestinal Endoscopy* **37:** 1383.

Box 3.8 Risk factors for post-ERCP pancreatitis

- Young, ♀.
- Suspected ➲ sphincter of Oddi dysfunction (SOD).
- Normal serum bilirubin.
- Previous ERCP-related pancreatitis.
- Difficult common bile duct (CBD) cannulation.
- contrast injection of pancreatic duct.
- Pre-cut (needle/knife) sphincterotomy.
- Pancreatic sphincterotomy.
- Balloon sphincter dilatation.

Cholangioscopy

Technique

Recent advances in endoscope technology now enable direct visualization of biliary and pancreatic ductal mucosa. Most widely used technology involves 10F (3.3mm diameter) single operator cholangioscope, which is inserted down the working channel of duodenoscope. Fine bore naso-endoscopes inserted orally are less frequently used. Under direct vision targeted biopsies and stone fragmentation may be performed.

Indications

- Assessment of indeterminant ➲ biliary strictures (allowing direct visualization and directed biopsies).
- Direct electrohydraulic lithotripsy for impacted bile duct stones (see ➲ choledocholithiasis).

Complications

Related to ERCP—see ⊳ 'Complications', p. 210. Prophylactic antibiotics given for cholangioscopy, in view of increased risk of cholangitis without this.

Endoscopic ultrasound (EUS)

EUS has become a valuable tool for diagnosis and therapy. Echo-endoscopes use sound waves for imaging tissue consistency and interfaces between tissue planes, and typically use higher frequencies than those in transabdominal US (results in better definition, but ↓ penetration). Three main types of echo-endoscope in use:

- **Radial echo-endoscope** has rotating US probe integrated into tip, and 270° or 360° images obtained in circumference perpendicular to endoscope tip. Main indications include staging of GI tract tumours in terms of local invasion and regional lymphadenopathy (especially ➲ oesophageal, ➲ gastric, and ➲ rectal cancer); and diagnosis in pancreatico-biliary disease (exclusion of ➲ choledocholithiasis, characterization of pancreatic lesions not seen on CT, and assessment of ➲ neuroendocrine tumours). In experienced hands, EUS for detecting mediastinal lymphadenopathy in oesophageal cancer has sensitivity 80% and specificity 90%.
- **Linear array echo-endoscope** provides images obtained along a plane parallel to endoscope axis. Fine needle aspiration (FNA) and biopsy (FNB) may be used for targeted sampling of mediastinal lymph nodes in lung cancer, pancreatic masses and ➲ pancreatic cystic tumours). Therapeutic indications include drainage of ➲ pancreatic pseudocysts, EUS-guided coeliac plexus nerve block in patients with pain due to ➲ chronic pancreatitis or ➲ pancreatic cancer. Doppler US capability allows vascular structures to be assessed (e.g. portal vein in pancreatic cancer staging).
- **Ultrasound probes** are thin and need to be advanced through channel of regular endoscope. Probes generally provide high-resolution circumferential view along same plane as radial echo-endoscope. Miniprobe US can be used in the assessment of ➲ biliary strictures, but do not allow tissue sampling.

Indications

- Tumour staging: oesophageal, lung, gastric, pancreatic. EUS more accurate than CT for locoregional staging of oesophageal cancer: important as superficial tumours limited to mucosa can undergo attempted endoscopic mucosal resection or ablation, while tumours extending through wall should be considered for preoperative chemoradiation. Patients with tumour involving submucosa or muscularis propria considered for surgical resection alone.
- Detection, diagnosis, and staging of pancreatic cancer, although multislice CT more sensitive for detecting portal vein invasion.
- Tissue acquisition.
- Assessment of submucosal lesions and pancreatic cystic lesions.
- Pancreatic pseudocyst drainage.
- Lumen apposing metal stent (LAMs) insertion (e.g. for gastroenterostomy).

Complications

- Similar to diagnostic endoscopy.
- FNA of pancreatic lesions associated with <2% complication rate (haemorrhage, infection, perforation, pancreatitis).

Colonoscopy

First used in the early 1960s, colonoscopy is now the standard technique for assessing and treating colonic disease. In expert hands, caecum can be visualized in 98% cases, and terminal ileum in 90%.

Making colonoscopy easier

Tortuosity and lack of landmarks remain issues. Variable-stiffness instruments can help negotiate difficult sigmoid loops and splenic flexures, and magnetic endoscope imaging (e.g. ScopeGuide) facilitates negotiation of loops, improves success rates, and shortens procedure times. See also ▷ bowel preparation.

Sedation

Need for and practice of sedation varies widely and depends on patient expectation as well as local practice. General anaesthesia used in some countries. Although some stretching of peritoneal attachments almost inevitable, with resulting visceral discomfort, total colonoscopy in unsedated patients is possible with expert endoscopists and motivated patients. Inhaled nitrous oxide (e.g. Entonox®) increasingly used to enable total colonoscopy without IV sedation.

In UK, routine practice involves IV administration of a benzodiazepine to provide anxiolysis and anterograde amnesia together with an opiate for analgesia. See also section above on ▷ sedation (p. 196).

Colonoscopy in pregnancy

Colonoscopy should be avoided in pregnancy unless very strong indications or life-threatening emergencies. It is probably safest in 2nd trimester,[5] but in 1st and 3rd trimester may be used to defer or as an alternative to surgery for evaluation of suspected colon cancer, uncontrolled severe colonic haemorrhage, colonic stricture of unknown cause, or colonic pseudo-obstruction. Otherwise, colonoscopy for elective indications, such as surveillance for prior history of colon cancer or colonic polyps, is usually deferred in any trimester until after delivery.

Contraindications

- Avoid if possible for 4–6wk after myocardial infarction.
- Colonoscopy contraindicated in acute or abscess-associated diverticulitis (risk of perforation).
- ➲ Crohn's disease, ➲ ulcerative colitis and ischaemic colitis mandate particular care but colonoscopy may provide valuable information (over sigmoidoscopy) and benefit may outweigh risk.
- See also ▷ antiplatelet therapy and anticoagulation, p. 199.

[5] Savas N (2014). *World J Gastroenterol* **20**: 15241–52.

Complications

Diagnostic colonoscopy has morbidity ~0.25% and mortality 0.02%. Therapeutic procedures have morbidity 1–7% and mortality 0.04%.

- **Perforation** may relate to:
    - Direct tip trauma (e.g. into colonic diverticulum) or endoscope looping during scope insertion. Rectosigmoid is the site of >60% of perforations. Splenic flexure also relatively common site of injury, and avulsion of ligaments attaching colon to spleen can cause significant haemorrhage.
    - Intervention. 0.3–1% of polypectomies. A 4–5% perforation rate is associated with balloon dilatation of colonic strictures, particularly with balloon diameter >25mm.
    - Free perforation into peritoneal cavity may occasionally be recognized during procedure, but usually diagnosis suggested by marked persistent abdominal distension or pain after procedure. Fever, and signs of shock and peritonitis may develop.
    - Retroperitoneal perforation may present with subcutaneous emphysema.
    - Plain AXR and erect CXR should be performed, and may show pneumoperitoneum. If normal but clinical suspicion remains, an abdominal CT should give diagnosis. Conservative management sufficient for most small perforations (NBM, IV fluids, IV antibiotics), but close inpatient review necessary, and surgery required in 25% (particularly if perforation large).
- **Bleeding**
    - Immediate bleeding is the most common complication of polypectomy. Most cases resolve spontaneously. Management includes injecting 5–10ml of 1:100,000 adrenaline (epinephrine) solution into stalk/submucosa or haemoclip placement (see also ➢ endoscopic haemostasis, p. 217). Angiography and even laparotomy occasionally required.
    - Delayed bleeding can occur up to 2wk after colonoscopy.
- **Post-polypectomy coagulation syndrome** presents with pain, peritonitis, and fever. Needs to be differentiated from perforation, as invariably settles with conservative management.
- **Splenic rupture** rare, but may present with pain, peritonitis, and hypovolaemic shock, with bloods showing acute anaemia and ↑ white cell count. Diagnosis made on CT. Laparotomy often required.

Flexible sigmoidoscopy

Procedure similar to colonoscopy, but results in examination of left colon only (up to splenic flexure). Bowel preparation usually with enema administered at home on morning of procedure or in hospital 30min prior to procedure, rather than full oral bowel preparation. Procedure can usually be done without IV sedation. Indications include investigation of anorectal disease (e.g. fresh rectal bleeding) and of diarrhoea. While majority of colonic polyps and cancers occur in left colon, the major limitation of flexible sigmoidoscopy is risk of missing proximal colonic lesion in patients with unexplained rectal bleeding or change in bowel habit. Complications from diagnostic flexible sigmoidoscopy very low, but interventions (e.g. polypectomy) carry same risks as when done during full colonoscopy.

Endoscopic interventions

Endoscopic dilatation

Mechanical dilatation of GI tract obstruction has been attempted for hundreds of years. Most common site for endoscopic dilatation is the oesophagus, with indications including benign peptic strictures (see ▶ Approach to dyspepsia and gastro-oesophageal reflux and ➲ caustic ingestion), ➲ oesophageal tumours, ➲ Schatzki rings, and ➲ achalasia. Course of dilatation provides good relief in >85% of patients with benign strictures due to reflux, but is less effective if stricture due to radiation or corrosives. Most gastric strictures occur at pylorus; causes include peptic ulceration, ➲ gastric cancer, and ➲ caustic ingestion. Duodenal strictures are usually due to extrinsic compression (e.g. ➲ pancreatitis, ➲ pancreatic cancer) and rarely due to duodenal carcinoma. Most common indication for small bowel or colonic endoscopic dilatation is ➲ Crohn's disease.

Types of dilator

- Fixed-diameter dilators ('➲ bougies') have long been used to dilate oesophageal strictures. Most dilators (e.g. Savary–Gillard) inserted over endoscopically placed wire. May have 20cm tapered tip, gradually widening to 5–20mm fixed diameter. Usual dilatation for benign strictures 16–18mm, but wider dilatation may be needed for ➲ Schatzki rings.
- Endoscopic dilatation in sites other than oesophagus almost exclusively performed using over-the-wire balloons. Balloons more expensive than push dilators, in part as single use. Can be inserted over wire and positioned either under imaging control or directly at endoscopy through scope (TTS). Balloon diameters vary from 4 to 40mm. Larger balloons (30–40mm) reserved for treatment of ➲ achalasia. Balloons exert direct circumferential pressure rather than shearing force exerted by bougies. Radial force exerted is less than with bougies and very rigid fibrotic strictures may be difficult to dilate with balloons.

Practice points

- Fluoroscopic screening may be needed with both techniques if stricture cannot be passed endoscopically. Balloons exert only radial force. Both methods are safe in hands of experienced endoscopist familiar with their use.
- See ➢ antiplatelet therapy and anticoagulation for guidance on managing these drugs (dilatation is high bleeding risk procedure). Consider prophylactic antibiotics for patients with high risk cardiac lesions).
- Overall oesophageal perforation rate 2.6%, mortality 1%, with ↑ risk for malignant strictures (6.4% perforation, 2.3% mortality). Other complications include bleeding and pulmonary aspiration.
- **How far to dilate**? Do not attempt routine oesophageal dilatation to >18mm (see earlier comment concerning Schatzki rings). For achalasia, be very cautious about use of 40mm balloon as this is associated with significantly higher risk of perforation. In colonoscopic balloon dilation, perforation rate higher with dilatations >25mm.

Argon plasma coagulation (APC, 'argon beamer')

Used for endoscopic treatment of bleeding and superficial mucosal lesions. Allows controlled non-contact electrocoagulation by high-frequency energy delivered to tissue through ionized gas. Application and control easier than for free beam lasers, but depth of tissue injury more superficial and not sufficient for relief of dysphagia associated with oesophageal carcinoma. Particular use for ➲ angiodysplasia, ➲ gastric antral vascular ectasia, and bleeding related to ➲ radiation damage.

Heater probe

Useful for treating actively bleeding ulcers within reach of endoscope, and also for lowering risk of bleeding of high-risk lesions. Keys to successful use include direct probe pressure to tamponade vessel, use of 25–30J setting, and repeated applications.

Electrocoagulation

Principle of using electrosurgical or diathermy currents in therapeutic endoscopy is to produce heat with resultant coagulation of blood vessels and facilitate tissue transection.

- **Cutting current** has uninterrupted waveform of low voltage. Relatively high power, but because low voltage less able to cross desiccated tissue and does not penetrate deeply.
- **Coagulating current** has intermittent high voltage spikes with intervening off periods lasting 80% of time. Allows deeper spread of current and less local tissue destruction.
- **Monopolar current** involves current flowing between wire of a snare loop or jaws of biopsy forceps and a patient plate.
- **Bipolar current** involves all current flowing from one side of snare to other, with attraction of much more localized effect.
- Local current density critically important and higher for bipolar electrosurgery, which is why bipolar favoured for local haemostasis.
- Heat produced relates directly to power settings on unit dial. Current recommendations are to perform polypectomy at low power setting (15–25W) to allow time to react to what is happening and avoid 'cheese-wiring' stalk.
- Monopolar electrocoagulation of upper GI bleeding lesions uncommon, having been replaced by bipolar electrocoagulation or thermal coagulation using ➢ heater probe, often in conjunction with adrenaline injection. See ➢ endoscopic haemostasis.

Endoscopic haemostasis *(see Plate 15)*

Endoscopic treatment ↓ rebleeding and mortality in patients with significant upper GI bleeding, but must be used in conjunction with effective resuscitation and additional medical therapies (see ▲ **acute upper GI bleed** ▲). Range of haemostatic modalities used for different clinical indications:

Oesophageal varices

Also see Section 6, 'Emergencies', p. 678 and ➲ portal hypertension.

Variceal band ligation (VBL)

- Varix sucked into short plastic sleeve at endoscope tip, and tight rubber ring applied around base (see Plate 8).
- Varix thromboses and sloughs off in <7d. Up to 7 bands can be applied.
- Complications include 'banding ulcers', but fewer side effects than sclerotherapy, so endoscopic treatment of choice for gastro-oesophageal varices.

Injection sclerotherapy

- Established longer than VBL.
- Involves injection of 1–4ml sclerosant (e.g. 5% ethanolamine) into or adjacent to varix.
- Like VBL, controls acute bleeding in 85–95% of cases, but risk of sclerotherapy ulcers, oesophageal stricture, mediastinitis, and perforation.

Gastric varices

- VBL and standard sclerotherapy not effective.
- Injection of other tissue adhesives (e.g. 2-cyanoacrylate) or thrombin may be effective.
- If bleeding not controlled, ➲ Sengstaken–Blakemore tube insertion and TIPSS (➲ transjugular intrahepatic portosystemic shunt) may be necessary, as for oesophageal varices.

Complications of variceal therapy: During acute variceal bleeding, endoscopy-related aspiration of blood/gastric contents is a serious complication (which may be avoided by prior endotracheal intubation—see ▲ **acute upper GI bleed** ▲). Following variceal therapy, complications reported in 10–15%: fever, retrosternal discomfort, and dysphagia usually resolve in <48h. Sclerotherapy-induced oesophageal ulceration common, but oesophageal perforation, mediastinitis, broncho-oesophageal fistula, and stricture formation rarely occur. Bacteraemia may lead to endocarditis in patients with prosthetic/diseased heart valves (see ▷ 'antibiotic prophylaxis', p. 198). VBL appears to carry significantly lower risk of oesophageal ulceration, mediastinitis, and perforation than sclerotherapy.

Bleeding peptic ulcers

Endoscopic therapy required for patients with active bleeding, visible vessel in ulcer base, or adherent clot. Techniques include:

- **Injection** ~4–10ml adrenaline (epinephrine) 1:10,000 injected around and then into bleeding point. Thrombin or fibrin injection also effective, but not widely used. A second modality, in addition to injection, gives best haemostatic results.
- **Heat** Options include heater probe, multipolar coagulation (BICAP; electrocoagulation) or APC. Heater probe includes powerful water jet to clear blood clot and achieves haemostasis via combination of compression of bleeding point and heat.
- **Mechanical clips** Range of products available and may be very effective at clipping clearly visible vessels.

- **Haemostatic powder spray** promising. Particularly useful in difficult to access areas (e.g. posterior duodenal bulb) or large areas of bleeding. Appears effective in isolated use, and in conjunction with traditional modalities, although definitive data awaited.

Post-polypectomy bleeds

As with ulcers, injection of adrenaline (epinephrine) into base of polyp stalk, followed by heater probe, may be effective, as may clip placement.

Angiodysplasia/vascular malformation/➔ gastric antral vascular ectasia (GAVE)

Application of heat, with ➢ heater probe, ➢ argon plasma coagulation (APC), or radiofrequency ablation (RFA) may be effective.

Polypectomy

- Endoscopic removal of polyps in GI tract possible by passage of snares or by endoscopic mucosal resection (EMR). Techniques of EMR beyond scope of this text, but depend on lifting polyp off submucosa with cushion of fluid containing 1:100,000 or 1:200,000 adrenaline, some indigo carmine, and small amount of a high molecular weight polymer such as hyaluronic acid, which extends period that fluid cushion can be used. Indications for EMR include large polyps and mucosal tumours.
- Conventional polypectomy safe in experienced hands but carries risk of 1 in 1,000 of perforation, and 1 in 100 of significant bleeding. Post-polypectomy bleeding can be ↓ by ligation of any stalk (especially if >10mm diameter) with an endoloop, or injection of polyp base with dilute 1/100,000 adrenaline.

Stents in the GI tract (see Fig. 3.2, Plates 21, 41 and 42)

- Endoscopically placed stents have led to significant advances in managing luminal strictures. Broadly, two types of stent available:
  - Polyethylene plastic stents are non-expanding and have fixed external diameters. Main use is within pancreaticobiliary system. Usually inserted at ERCP. Within biliary tree, 7–10F straight or pigtail stents generally used. These often maintain biliary drainage for 3–6mo, but can be readily replaced if necessary. May be used for benign or malignant disease. 3–5F stents often placed within pancreatic duct to ↓ risks of post-ERCP pancreatitis in high-risk patients.
  - Self-expanding mesh-metal stents (SEMS) inserted under fluoroscopy in collapsed form, within a sheath, and over guidewire. After withdrawal of sheath, stent expands and is deployed. SEMS have increasing role in management of malignant oesophagogastric, duodenal, biliary, and colonic strictures, with successful placement in >95% of cases. Enteral/colonic stents expand to 20–25mm in their central portion, with flanges at both ends, and biliary stents expand to 6–10mm. SEMS should generally be used only for malignant strictures, as tissue ingrowth through mesh makes subsequent removal difficult/impossible. Development of covered SEMS has reduced this problem, and broadening role to management of fistulae and benign stricturing disease, as subsequent removal may be possible for up to 12 months post-insertion.
- Complications following enterally placed SEMS in 9–30% of cases, and include perforation, bleeding, stent migration, and occlusion. Perforation in 2–4%, but significantly higher if pre-stent dilatation.

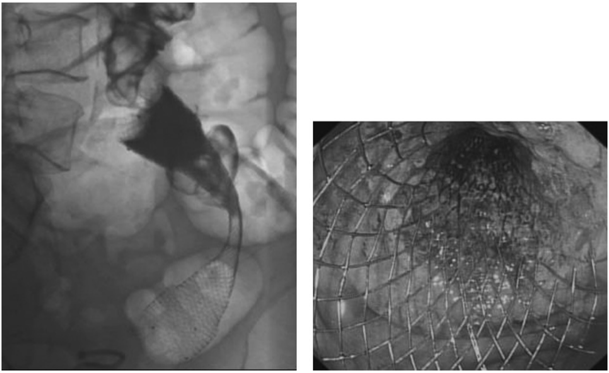

Fig. 3.2 Mesh-metal colonic stent for malignant obstruction.

Laser therapy and the GI tract

Bleeding peptic ulcers

Argon and Nd:YAG lasers were the first endoscopic therapies for haemostasis to be assessed in large randomized controlled trials. Showed that lasers stop bleeding and ↓ rebleeding, but expensive and cumbersome ∴ replaced by more portable methods (see ➢ heater probe and ➢ argon plasma coagulation).

Oesophageal carcinoma

- Endoscopic laser is non-contact method of thermally ablating tumours: enables tissue vaporization and coagulation necrosis. Tissue effects vary with wavelength: Nd:YAG, KTP, and argon lasers have been used. Luminal patency and relief of dysphagia achieved in 70–85% of patients, with 25% symptom free at 3mo. Usually maximum patency achieved in 2–3 sessions. Minor side effects: chest pain, odynophagia, low-grade fever, and leukocytosis. Major side effects: perforation (2%), fistula or bleeding (1%), and sepsis (0.5–1%).
- Characteristics favouring successful lasering include exophytic and straight short tumour (<6cm), rather than extensive angulated masses.

Other applications of laser in GI tract

Laser therapy has been used to ablate ➲ Barrett's oesophagus. Multiple treatments required and perforation has been reported. Lasers have been used to treat non-surgically resectable colonic cancers and polyps, but this has declined recently. Endoscopic stenting has become more popular for malignant growths, and techniques of endoscopic mucosectomy for large benign sessile growths have advanced rapidly.

Chromoendoscopy

First described in Japan in 1976. Endoscopic spraying of GI tract with contrast dyes can highlight subtle irregularities in mucosa, improving sensitivity of endoscopic examination, particularly for pre-neoplastic and neoplastic lesions. Stains may be vital (absorptive), contrast, or reactive. Vital stains (Lugol's iodine, methylene blue) enter cells by preferential absorption, contrast stains (indigo carmine) seep into mucosal interstices to highlight mucosal topography, and reactive stains react chemically with cellular constituents.

Recent developments in high-resolution and magnifying endoscopy appear to enhance diagnostic usefulness of chromo-endoscopy. Different staining patterns of ➔ colonic polyps have been categorized (e.g. the five pit patterns described by Kudo—see Plates 29 to 34), and allow improved endoscopic prediction of histology. However, current systems too cumbersome for routine use. Most promising techniques are detection of squamous cell cancer of oesophagus (see ➔ oesophageal tumours) with Lugol's solution (this iodine-based dye has affinity for glycogen in non-keratinized squamous epithelium), staining of ➔ Barrett's oesophagus by methylene blue (including potential to identify neoplasia) and demarcation of neoplasia in stomach and colon with indigo carmine for local endoscopic resection. Indigo carmine (0.1%) sprayed onto colonic mucosa increases yield of endoscopic detection of neoplastic lesions in ➔ ulcerative colitis and enables targeted biopsy of suspicious lesions.

Section 4

An A to Z of gastroenterology and hepatology

A

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Abetalipoproteinaemia

Autosomal recessive disorder of lipid metabolism resulting from mutation in microsomal triglyceride transfer protein (*MTTP*) or *APOB* (causes hypobetalipoproteinaemia). Rare: <1/million. Characterized by **steatorrhoea**; **malabsorption** of fat-soluble ➲ vitamins A, D, E, and K; ataxia; retinitis pigmentosa; compromised posterior column function; and acanthocytic erythrocytes. Reduced synthesis of apolipoprotein B leads to absence of chylomicrons, LDL, and VLDL. Small intestinal biopsy shows lipid droplets in intestinal epithelial cells. Can develop hepatic steatosis (see ➲ non-alcoholic fatty liver disease). Gene sequencing confirms diagnosis. Treatment involves low fat diet (<30% caloric intake) and minimizing long-chain fatty acid consumption. Early treatment with high-dose oral vitamins E (100–300mg/kg/d) and A (100–400IU/kg/d) mitigates neuropathy and retinopathy. Often require regular vitamin D (800–1200IU/d) and K (5–35mg/wk).[1]

Acetaminophen

See: ➲ paracetamol overdose.

Achalasia

Oesophageal motor disorder characterized by failure of relaxation of lower oesophageal sphincter (LOS) and loss of peristalsis of oesophageal body, leading to functional obstruction at lower end of oesophagus, food stasis, and oesophageal dilatation. Risk of **squamous cell cancer** (see ➲ oesophageal tumours), presumably due to stasis of food and mucosal irritation.

Aetiology

Ganglion cells of myenteric plexus ↓ but cause unknown. Viruses and autoimmune mechanisms have been proposed. Non-adrenergic non-cholinergic inhibitory innervation (mostly nitric oxide mediated) impaired, which mediates sphincter relaxation.

Clinical features

Dysphagia to both solids and liquids, regurgitation, weight loss, and chest pain (may relate to oesophageal spasm). Most common age of onset: 30-50y.

Investigation

Diagnosis made on basis of history, radiological, endoscopic, and manometric findings.

- CXR may show air–fluid level in dilated oesophagus (Fig. 4.1).
- Barium swallow shows dilated oesophagus with reduced peristalsis.
- Endoscopy essential in all patients to exclude mucosal pathology and pseudo-achalasia (oesophageal dilatation and dysphagia which mimics achalasia, but usually due to malignant obstruction).

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[1] Lee J & Hegele RA (2014). *J Inherit Metab Dis* **37**: 333–9.

- ▷ Oesophageal manometry shows ↑ lower oesophageal sphincter pressure and incomplete or absent sphincter relaxation.
- Differential diagnosis: oesophageal spasm, ➲ trypanosomiasis (Chagas' disease), and ➲ pseudo-achalasia.

Management

Aim is to ↓ pressure gradient across LOS.

- **Drugs** do not work well, and primarily indicated in patients where more invasive interventions not possible.
  - Nitrates and calcium channel blockers provide, at best, short-lived effects on LOS pressure, and have side effects.
  - → BOTULINUM TOXIN injected into sphincter ↓ pressure and relieves symptoms. Short-lived, and repeat injections necessary every 6–12mo.
- **Endoscopic dilatation**. Performed using 30, 35, or 40mm balloons passed over guidewire. Balloon inflated for 1–2min. Good response in 60–70%, but many need >1 procedure, and some consider long-term outcome inferior to surgery. Complications include perforation (1–5%, more common with larger balloons) and reflux (≈10%). Initial dilatation with aim of achieving resting LOS pressure <15mmHg (with surgery for short-term failures) gives good long-term results in >70% and treatment satisfaction in >80% patients.[2]
- **Surgical myotomy** effective in 90% but causes reflux in 10%. Antireflux procedure (such as partial fundoplication) often done at same time. Laparoscopic Heller myotomy treatment of choice.
- **Peri-oral endoscopic myotomy (POEM)**. Recently described innovation, involving endoscopy-directed submucosal dissection. Endoscopic incision made into wall of lower oesophagus, and endoscope tunnelled down to LOS. Here, sphincter muscles are cut with endoscopic knife. Incision into oesophagus closed with clips. Only available in specialist centres, where 82–100% success, and 10% complication rate (bleeding, full perforation, infection).

Achlorhydria

Defined as failure of intragastric pH to fall below 4 under stimulation with pentagastrin. In absence of gastric acid, negative-feedback control of gastrin lost and hypergastrinaemia results (Box 4.1). Achlorhydria leads to overgrowth of nitrosamine-producing bacteria with potential carcinogen activity. ➲ Gastrinoma (Zollinger–Ellison syndrome) may be suspected and acid secretory studies may be necessary. Atrophic gastritis may be associated with ↓ intrinsic factor secretion (see ➲ pernicious anaemia).

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[2] Hulselmans M *et al.* (2010). *Clin Gastroenterol Hepatol* **8**: 30–5.

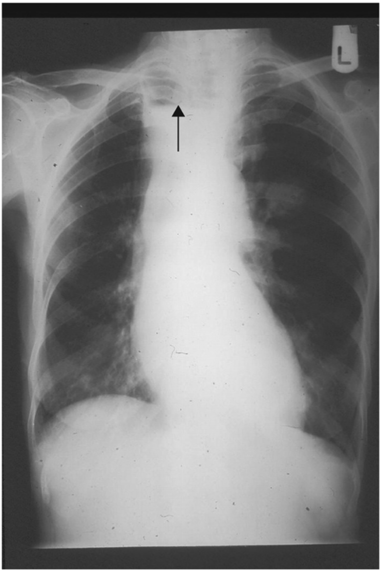

Fig. 4.1 CXR in patient with achalasia, showing air–fluid level (arrowed) within dilated oesophagus.

Box 4.1 Causes of achlorhydria

- ➲ Atrophic gastritis.
- Autoimmune (➲ pernicious anaemia).
- Environmental (➲ *Helicobacter pylori*).
- Mucolipidosis type 4. Crippled parietal cells due to absent protein needed for vacuolar trafficking.
- Previous gastrectomy or vagotomy.
- Rare tumours that produce hormones inhibiting acid secretion (e.g. somatostatinoma—see ➲ pancreatic endocrine tumours).
- Severe hypocalcaemia (impairs parietal cell acid secretion).
- Acid secretion ↓ in AIDS.

Acquired immune deficiency syndrome

See: ➲ HIV and the gut and ➲ HIV and the liver.

Acromegaly and GI tract

- Risk of ➲ colonic polyps and ➲ colon cancer in acromegaly (prevalences ≈25% and 5%, respectively). British Society of Gastroenterology guidelines (2010) 🖱 http://gut.bmj.com/content/59/5/666.long recommend initial screening by colonoscopy at age 40, repeated every 5–10y (3y if ↑ risk: adenoma at 1st colonoscopy or ↑ serum IGF-1 levels).
- Colonoscopy often difficult due to long redundant colon. Conventional bowel preparation less effective, and double quantities (preferably of osmotically active polyethylene glycol-based solutions such as Klean-Prep®) suggested.
- Clinical enlargement of spleen, liver, or kidneys unusual and warrants further investigation. Other GI complications include macroglossia, and those arising as side effects from use of the somatostatin analogue → OCTREOTIDE (used as suppresses growth hormone secretion and can shrink proportion of pituitary tumours because of their high somatostatin receptor density).

Actinomycosis

Subacute or chronic granulomatous disease due to variety of fermentative branching, filamentous bacteria, causing multiple abscesses and draining tracts. Commensal organisms, which reside on mucosal surfaces. Active tissue invasion requires disruption of epithelial barrier through surgery, trauma, foreign bodies, ischaemia, or prior infection by other organisms. Can occur in immune competent and compromised patients. Abdominal involvement rare, and usually associated with perforating/fistulating GI conditions (appendicitis, diverticulitis, surgery, foreign bodies such as fish bones or intrauterine contraceptive devices). May present as slow growing tumours. Classically, sinus tracts contain sulphur granules. Diagnosis made by culture, microscopy, and (increasingly) 16S rRNA analysis. Most lesions have polymicrobial co-infection. Antibiotic treatment includes IV benzylpenicillin (± metronidazole or aminoglycoside such as gentamicin) to cover mixed infections; duration >2wk, guided by clinical response.[3]

Acute fatty liver of pregnancy (AFLP)

Epidemiology and pathogenesis

Rare mitochondrial cytopathy, affecting 1:10,000–20,000 pregnancies. Microvesicular fatty infiltration of hepatocytes, and a ❗ medical and obstetric emergency, with ↑ maternal and foetal mortality. Unlike other liver conditions specifically related to pregnancy (➲ HELLP syndrome and ➲ obstetric cholestasis), frequently associated with ▲ **acute liver failure** ▲.[4] Pathogenesis unclear, but associated with inherited long-chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD) deficiency. Risk factors include 1st and twin pregnancies.

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[3] Könönen E & Wade WG (2015). *Clin Microbiol Rev* **28**: 419–42.

[4] Joshi D *et al.* (2010). *Lancet* **375**: 594–605.

Clinical features

- Usual presentation at 34–37wk of pregnancy. Rare before 20wk or after delivery.
- Characteristic presentation with nausea, vomiting, abdominal pain, and confusion, with pre-eclampsia (thirst, headache, blurred vision, proteinuria, hypertension, peripheral oedema).
- Jaundice common (in contrast with ➲ HELLP syndrome), with additional features of ▲ **acute liver failure** ▲ (hypoglycaemia, bleeding, ▲ **hepatic encephalopathy** ▲). Pruritus may be initial symptom and, rarely, clinical overlap with ➲ obstetric cholestasis seen. Diabetes insipidus reported.
- Rise in serum ammonia and lactic acidosis in severe disease.

Investigation

See also ► Approach to liver problems in pregnancy.

- Blood results may show ↑ WCC, ↑ AST/ALT (but usually <750IU/L), ↑ Bn 6–8× ULN (i.e. ~100μmol/L). ↑ PT suggests significant liver impairment; ↑ uric acid, ↑ urea, and ↑ creatinine also common. Viral serology mandatory.
- US should be performed, in part to exclude other conditions (e.g. biliary obstruction, subcapsular haematoma), but no diagnostic features of AFLP.
- Liver biopsy shows microvesicular fat but rarely performed during pregnancy.

Management

- Intensive care setting with specialist hepatology and obstetric input essential. Prompt delivery is the cornerstone of treatment, with management of ▲ **acute liver failure** ▲ and ▲ **hepatic encephalopathy** ▲ as necessary.
- DDAVP may be required for diabetes insipidus.
- ➲ Liver transplantation has been successful, but rarely required unless delivery delayed.

Prognosis

- Maternal mortality <1% with specialist care. Perinatal mortality 7%.
- Mother, infant, and father should be tested for predisposing genetic mutations.
- Chronic liver disease does not develop following AFLP.

Acute intermittent porphyria

See: ➲ porphyrias.

Acute pancreatitis (AP)

Epidemiology and pathogenesis

Incidence: 5–25/100,000). ➲ Alcohol dependency and ➲ gallstones account for most cases (Table 4.1). Absence of chronic changes on imaging differentiates from ➲ chronic pancreatitis, but clinical distinction from acute-on chronic pancreatitis may be difficult.

Clinical features

Severe unremitting epigastric pain radiating to back, with nausea and vomiting. Patient may be shocked. Bruising on flanks ('Grey Turner sign') or umbilical area ('Cullen's sign') in 1%, and indicates haemorrhagic pancreatitis with poor prognosis. ➲ Ileus common.

Complications

- **Local** Inflammatory mass, acute necrotic collection (ANC), walled off pancreatic necrosis (WOPN) (usually occurs >4wk after acute episode), ➲ pancreatic pseudocyst, pseudo-aneurysm, obstructive jaundice, gastric outflow obstruction, ➲ portal vein thrombosis.
- **Systemic** Sepsis, pleural effusion, acute respiratory distress syndrome, multiorgan failure, disseminated intravascular coagulation.

Severe AP usually associated with pancreatic necrosis (20–30%). Infected necrosis occurs in 30–70% of latter, and accounts for >80% of deaths.

Investigation

- Blood tests:
  - FBC, U&E, LFT, Glu, Ca, bicarbonate essential (Table 4.2) for detecting complications and prognostic scoring.
  - Serum ALT/AST >150U/L >95% specific for ➲ gallstones, rather than alcohol, as cause of AP. Check lipid profile for hypertriglyceridaemia (especially concentrations >11.3mmol/L).
  - CRP reflects severity of inflammation (in absence of infection).
  - ↑ Serum ➤ **amylase** makes diagnosis (>1,000U/L in appropriate clinical setting), but poor correlation with severity. Sensitivity ↓ if symptoms present >24h. Very occasionally helpful to measure urinary amylase, particularly if diagnostic uncertainty with possible macroamylasaemia (not filtered at glomerulus, so urinary amylase normal) or severe hyperlipidaemia (where serum lipid fraction can interfere with biochemical tests).
  - Serum lipase has longer $t_{1/2}$ (↑ for up to 12d), and more specific), therefore may support diagnosis if delayed presentation.
- Plain AXR may show 'sentinel loop' due to local small bowel ileus. Pleural effusion on CXR correlate with severe disease.
- US should be performed as soon as possible to look for obstructing gallstones/dilated ducts, but often difficult views due to dilated small bowel loops.
- Contrast-enhanced CT should be performed 48h **after** clinical onset, unless pancreatitis clinically mild. Necrosis predicts prolonged course and potential mortality (see Table 4.3), but may not be seen in 1st couple of days after onset. CT also defines peri-pancreatic inflammation, and evidence of chronic pancreatitis (e.g. calcification).

- MRCP may define pancreatic duct disruption, or biliary obstruction in case of difficult US.
- Various scoring systems validated (e.g. Ransom/Glasgow/APACHE II/BISAP), but none 100% reliable and may be hampered by need for assessment at 48h. Best at predicting patients with mild disease, rather than those at risk of severe episode. High serum CRP (e.g. >210mg/L at 48–72h) highly sensitive for necrotizing pancreatitis. Outcome-closely linked to number of extrapancreatic organ failures.

Table 4.1 Causes of acute pancreatitis

- ➔ Gallstones/sludge (35%).
- Alcohol (30%).
- Hypertriglyceridaemia (1–10%, higher in gestational AP).
- Post-▶ ERCP.
- Ampullary disease: (e.g. stenosis, ➔ sphincter of Oddi dysfunction).
- Hypercalcaemia.
- ➔ Pancreatic cancer.
- Hypothermia.
- Drugs (e.g. HAART for HIV, azathioprine, NSAIDs, valproate, steroids).
- ➔ Pancreas divisum.
- ➔ Hereditary pancreatitis.
- Type 1 (IgG4-related) or type 2 ➔ autoimmune pancreatitis.
- Infection (e.g. mumps, Coxsackie, *Ascaris*, *Clonorchis*).
- Scorpion venom.
- Trauma.
- Cause unknown/idiopathic (30%).

Table 4.2 Modified Glasgow criteria*

WCC $>15 \times 10^9$/L	Urea >16mmol/L
Glucose >10mmol/L	Ca^{2+} <2mmol/L
LDH >600IU/L	Albumin <32g/L
AST >200IU/L	Pao_2 <8kPa

*The more factors present, the worse is the prognosis.

Table 4.3 Correlation of pancreatic necrosis with AP outcome

CT finding	Morbidity (%)	Mortality (%)
Necrosis	82	23
No necrosis	6	0

Management

- Expert MDT supportive therapy paramount, particularly prompt intensive care for those who need it.
- Intravascular volume expansion vital as large losses due to ileus and ‘3rd spacing’ in peri-pancreatic tissue.
- Analgesia (→ OPIATES usually required).
- Enteral feeding has key role in management and may ↓ bacterial translocation in moderate-severe pancreatitis. Start within 72h at slow rate, as tolerated.
- Evidence suggests no ↓ mortality with prophylactic antibiotics. If clinical suspicion of infection, take cultures urgently (including aspiration of necrotic collections) and give IV antibiotics as guided by local microbiology team.
- Early ANC rarely require intervention, but this may be necessary after 4wk for walled-off pancreatic necrosis (WOPN) or pseudocysts, particularly if infected or causing obstructive symptoms. Focus on minimally invasive approaches (e.g. percutaneous radiological drains, EUS-guided cyst drainage ± endoscopic necrosectomy), and away from open surgery. All decisions should be made through a specialist multidisciplinary pancreatic team.
- Urgent ERCP + sphincterotomy for presumed gallstone pancreatitis only clearly indicated if definite ➲ cholangitis or obstructive jaundice. ERCP not advised in all cases of gallstone pancreatitis, as may worsen pancreatitis further, and stones already passed in 80%. In gallstone pancreatitis, cholecystectomy (see ➢ p. 184) should be performed as soon as AP is settled (prior to discharge).
- In hypertriglyceridaemic pancreatitis, case series suggest efficacy of unfractionated heparin (increasing lipoprotein lipase, infuse at 600U/h, monitor APTTR) and insulin (0.1–0.3U/kg/h, monitor blood glucose and potassium, and supplement as necessary) infusions, and plasma exchange. Once pancreatitis has resolved, review the need for long-term lipid lowering therapy, usually with fibrate (e.g. bezafibrate 200mg PO tds) or omega-3-acid ethyl esters.

Prognosis

- 5–10% overall mortality with 1st episode of AP (which is 10× more likely to lead to organ failure than recurrent episodes). Obesity linked with more severe course, as is alcohol (even if this is not the primary cause). Half of deaths occur in 1st 14d.

Adenovirus

- Serotypes 31, 40, and 41 of subgenus F of this large family of dsDNA viruses, known as enteric adenoviruses, cause acute watery diarrhoea in infants and children. Incidence 4–10% in developed countries, 2nd in importance to rotavirus as viral cause of infectious diarrhoea. Rare in adults (1–5% of gastroenteritides).
- Can be persistent and severe in the immunocompromised. Non-enteric adenovirus types have been found in AIDS patients with diarrhoea.

- Symptoms include watery diarrhoea and vomiting. High fever unusual. Diagnosis requires PCR or electron microscopy. Incubation 8–10d, illness duration 5–12d, and virus shed in stool for 10–14d.
- No specific treatment. Goal is to prevent dehydration and maintain nutritional intake. Short-term complications include lactose intolerance and malabsorption. See also ▶ Approach to acute diarrhoea.

Afferent loop syndrome

- One of a number of ➲ post-gastrectomy syndromes, usually associated with ➢ Billroth II (Polya) gastrectomy (see ➢ p. 183 and ➲ dumping). Afferent loop (segment of small intestine leading to stomach) can fill with bile, particularly when gallbladder contracts after meal. Causes upper abdominal pain after meals, often relieved by vomiting bilious fluid. Obstruction may be caused by stenosis of anastomosis, adhesions, twisting of intestinal loop, and rarely by tumour, stones, or enteroliths.
- Diagnosis made by showing dilatation of afferent loop and site of obstruction. Dependent on surgical anatomy, diagnosis may be achieved by barium study, CT, or MRI.

Alagille's syndrome

Autosomal dominant form of intrahepatic cholestasis (1/100,000 live births), characterized by multisystem abnormalities (hepatic, renal, cardiac, facial, skeletal, and ocular). Classical features include butterfly vertebrae, triangular face, high forehead, and saddle-shaped nasal bridge. May present with persistent cholestasis, pruritus, hepatomegaly, and failure to thrive due to severe gastro-oesophageal reflux (see ▶ Approach to dyspepsia and gastro-oesophageal reflux) and malabsorption due to ➲ pancreatic insufficiency. Treatment involves intensive nutritional support and, although normal liver function regained in 50% by adolescence, others require ➲ liver transplantation.

Alcoholic liver disease

> **'Long quaffing maketh a short lyfe'**: John Lyly (1554–1606)
>
> **'Alcohol is the cause and the solution to many of life's problems'**: Homer Simpson (1956–)

Epidemiology and pathogenesis

- Alcohol accounts for 4% of disease burden worldwide, 3.2% of deaths, 1 in 6 of all emergency admissions in UK, and 40–80% of cases of cirrhosis in developed world. Consumption usually reported as units (1U = 1 small glass of wine, 0.5 pint/270ml of 4% beer, or single measure of 40% spirit). Safe limit debated, but currently in UK set at 14U/wk (for both ♂ and ♀). 6–8% of individuals drinking >40U/wk will develop cirrhosis within 12y, with 20–30% of long-term heavy drinkers developing significant liver disease.

- Alcohol excess very strongly linked to antisocial behaviour and domestic violence. Risks of binge drinking among young people increasingly recognized. See also ➲ alcohol use disorder.

Clinical features

A number of clinical patterns of disease occur.

Alcohol-induced steatosis

Results from heavy intake over months. Usually asymptomatic, but associated with hepatomegaly, mildly ↑ transaminases, and ↑ liver echogenicity on US. History should allow differentiation from ➲ non-alcoholic fatty liver disease (NAFLD). Although usually resolves after several weeks of abstinence, progresses to cirrhosis in 20% who continue to drink, and very rarely causes ▲ **acute liver failure** ▲.

Alcoholic steatohepatitis

Histological features include inflammation and necrosis (ballooning hepatocytes), necro-inflammation, Mallory bodies, neutrophilic infiltration, and mega-mitochondria. Likely to progress to cirrhosis.

Alcoholic hepatitis

Usually develops in those drinking very large amounts over long periods, although can occur earlier in course of misuse. An undefined trigger (usually develops in absence of recent ↑ intake) initiates severe inflammatory response associated with oxidant injury and neutrophilic liver infiltration. In those who recover, cirrhosis develops in >10%/y.

Clinical features

Acute onset of malaise, jaundice, anorexia, diarrhoea, and nausea. Tender hepatomegaly and signs of decompensated liver disease (e.g. ascites, ▲ **hepatic encephalopathy** ▲), which may worsen after hospital admission despite stopping alcohol. Malnutrition common and correlates with poor prognosis: >50% total energy intake in these patients comes from alcohol. Mortality 60%, related to sequelae of liver failure: sepsis, renal failure, and variceal bleeding.

Investigations

- FBC may show ↑ WCC (50% cases), ↓ platelets (direct toxic alcohol effect, and/or evidence of hypersplenism), ↑ MCV.
- U&Es may show ↓ Na^+, K^+, Ca^{2+}, Mg^{2+}. Renal failure may be due to sepsis, dehydration, or ➲ hepatorenal syndrome.
- LFTs: AST/ALT characteristically <3× ULN, with AST>ALT in >70%. ↑ bn and PT, incorporated into discriminant function (DF) test (Box 4.2), predicts mortality: DF >32 correlates with >35% 4wk mortality, but does not differentiate alcoholic hepatitis from end-stage liver failure/cirrhosis. Model for End-stage Liver Disease (MELD) score may be better predictor of severity in alcoholic hepatitis (Box 4.2).
- Acute phase markers (CRP, ferritin).
- ➢ Liver biopsy establishes diagnosis (and excludes/identifies underlying cirrhosis), with features of hepatocyte, ballooning, necrosis, Mallory bodies, and neutrophil infiltrate.

Box 4.2 Discriminant function (DF) and MELD score

DF in alcoholic hepatitis

DF = 4.6 × (prolongation of PT (sec)) + [(Bn (μmol/L))/17.1]
Consider corticosteroids if DF >32 (see text)

Model for end-stage liver disease (MELD score)

$3.8 \log_e(\text{Bn}(\text{mg/dl})) + 11.2 \log_e(\text{INR}) + 9.6 \log_e(\text{creatinine (mg/dl)})$

Management

- General supportive measures paramount, with diligent care of IV lines and prevention of sepsis. No role for antibiotic prophylaxis (fever, ↑ WCC, and ↑ CRP may be features of alcoholic hepatitis *per se*), but culture of blood, urine, ascites, and use of broad-spectrum antibiotics (e.g. 3rd-generation → CEPHALOSPORIN + METRONIDAZOLE or → PIPERACILLIN/TAZOBACTAM) essential if clinical sepsis, ideally guided by culture results. If sepsis continues, consider systemic antifungal treatment (e.g. fluconazole, amphotericin). See → ANTIBIOTICS and → ANTIFUNGALS.
- Insert urinary catheter and monitor output if impaired renal function.
- Fluid challenge. 250ml boluses of crystalloid (0.9% saline or Hartmann's). Avoid 5% glucose.
- Vitamin K 10mg IV for 3d.
- IV Pabrinex® (prophylaxis against ➔ Wernicke's encephalopathy).
- Nutritional support. High calorie supplements and protein supplements (>1.2g/kg/d) speed nutritional recovery, and do not appear to precipitate/ worsen encephalopathy. Parenteral feeding should be avoided if possible because of risks (sepsis, bleeding). NG feeding can be given safely (and probably reduces bacterial translocation).
- Role of → CORTICOSTEROIDS controversial. Previous consensus was for use (e.g. prednisolone 40mg od) in severe disease (DF >32) with encephalopathy but data from STOPAH trial demonstrated no benefit in long-term survival (despite possible advantage in 28d mortality on secondary analysis).[5] If used, response monitored using Lille score http://www.lillemodel.com/score.asp (score <0.45 at d7 of steroid therapy suggestive of responsiveness). Treatment should be interrupted in infection supervenes.
- Specific management of complications may be necessary. See:
  - ▶ Approach to ascites.
  - ➔ Hepatorenal syndrome.
  - Variceal bleeding—see ▲ **Acute upper GI bleeding** ▲.
  - ▲ **Hepatic encephalopathy** ▲.
  - ➔ Alcohol withdrawal and delirium tremens.
- → ACETYLCYSTEINE has shown some promise, and ➔ liver support devices used in clinical trials but exact role yet to be defined. Efficacy of pentoxifylline disproven by STOPAH trial.
- Emerging experience from France on role of liver transplantation in alcoholic hepatitis promising.

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[5] Thursz MR *et al.* (2015). *N Engl J Med* **372**: 1619–28.

Alcoholic cirrhosis

Clinical features of cirrhosis due to alcohol similar to those of other causes, ranging from asymptomatic to severely decompensated liver failure (see ► Approaches: Well patients with abnormal liver tests; ► Recent-onset jaundice; ► Cirrhosis and chronic liver disease). Histology may show micronodular cirrhosis. In alcoholic cirrhotics with ascites, 5y survival 16–25%. Mortality at 5y ↓ by 50% through abstinence, irrespective of degree of liver dysfunction. Death occurs due to complications of cirrhosis, including ➔ hepatocellular carcinoma.

Management includes patient education as to effect of abstinence on prognosis, and management of complications of cirrhosis. See:

- ➔ Portal hypertension.
- ▲ **Acute upper GI bleeding** ▲.
- ▲ **Hepatic encephalopathy** ▲.
- ➔ Hepatorenal syndrome.
- ► Approach to ascites.
- ► Approach to cirrhosis and chronic liver disease.

Most centres require patients to be abstinent for at least 6mo prior to ➔ liver transplantation, although 5y survival post-transplantation equivalent for those with alcoholic and non-alcoholic indications.

Alcohol use disorder

Epidemiology

Alcohol is the 3rd leading cause of preventable death in Europe and USA (behind smoking and obesity). Lifetime prevalence of dependency ~10% in ♂ and 4% in ♀. Each year, alcohol misuse costs UK economy >£25 billion and results in >1 million hospital admissions.

Clinical features

As well as ➔ alcoholic liver disease, most other systems are damaged: gastrointestinal (➔ oesophagitis, ➔ gastritis, ➔ acute and ➔ chronic pancreatitis); neurological (cortical atrophy/dementia, ➔ Wernicke's encephalopathy, peripheral neuropathy); endocrine (pseudo-Cushing's, diabetes mellitus, hypoglycaemia, alcoholic ketoacidosis, hypoandrogenization); cardiovascular (dilated cardiomyopathy, conduction defects); haematological (anaemia: see Box 4.3), and musculoskeletal (proximal myopathy, osteoporosis, ↑ falls risk). Important cause of malnutrition, and ↑ risk of range of malignancies (e.g. ➔ oesophageal/➔ gastric cancer, ➔ hepatocellular, bladder carcinoma).

Box 4.3 Causes of anaemia in alcohol-dependent patients

- ▲ **Acute upper GI bleeding** ▲.
- Iron deficiency secondary to chronic GI blood loss.
- ➲ Vitamin B_{12} deficiency.
- ➲ Folate deficiency.
- Macrocytosis of chronic liver disease.
- Hypersplenism.
- Bone marrow suppression.
- Acquired sideroblastic anaemia.
- Haemolysis (➲ Zieve's syndrome).

Assessment

- Dependency not defined by given quantity of alcohol consumed, but on resultant behaviours and their consequences.
- On examination, features of chronic liver disease may be present (see ▷ p. 131).
- Although blood tests may suggest alcohol excess (↑ AST>ALT, ↑ γGT, ↑ MCV, ↓ platelets), at least 2 of the 11 DSM-V criteria for alcohol use disorder should be met (Box 4.4).

Box 4.4 DSM-V criteria for alcohol use disorder

- Alcohol taken in larger amounts/over longer period than intended.
- Persistent desire or unsuccessful efforts to cut down or control use.
- Great deal of time spent in activities necessary to obtain or use alcohol, or recover from effects.
- Craving, or strong desire or urge, to use alcohol.
- Recurrent alcohol use resulting in failure to fulfil major role obligations at work, school, or home.
- Continued use despite persistent or recurrent social or interpersonal problems, caused or exacerbated by effects of alcohol.
- Important social, occupational, or recreational activities given up or reduced because of use.
- Recurrent use in situations in which it is physically hazardous.
- Use continued despite knowledge of having persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by alcohol.
- Tolerance, as defined by either need for markedly increased amounts to achieve intoxication or desired effect, or markedly diminished effect with continued use of same amount.
- Withdrawal, manifested by either characteristic withdrawal syndrome, or alcohol (or closely related substance such as benzodiazepine) taken to relieve or avoid ➲ alcohol withdrawal symptoms.

Management

Many physicians have a nihilistic view towards patients with alcohol dependency but a number of interventions are of benefit. Aim is to stop alcohol consumption or ↓ to manageable levels (complete cessation usually most effective goal in patients with dependency).

- Psychological assessment and support is the cornerstone of treating dependency. First step involves unequivocal clarification of problems being caused by alcohol, and assessment of patient's 'readiness for change'.
- Specialist alcohol support agencies available (e.g. Alcoholics Anonymous), and patient should be given clear details of how to access.
- Range of medications have been used to maintain abstinence in conjunction with psychological input, including disulfiram (causes nausea and vomiting with coincident alcohol) and acamprosate (stimulates GABA transmission and maintains abstinence in 12–18% of patients, compared with 5–7% on placebo).
- In patient with severe physical dependency (e.g. marked withdrawal symptoms), who is committed to stopping, admission to hospital for acute detoxification may be indicated, and ➲ alcohol withdrawal pre-empted and treated prophylactically.
- Alcohol Use Disorders Identification Test (AUDIT) 🖱 http://www.patient.co.uk/doctor/alcohol-use-disorders-identification-test-audit more sensitive than CAGE questionnaire; harmful drinking is indicated by score >15; score >20 is suggestive of dependency.

Alcohol withdrawal and delirium tremens (DT)

Abrupt cessation of alcohol in patients with a history of chronic excess use (see ➲ alcohol use disorder) may lead to clinical features that, in severest form, carry significant mortality. On stopping alcohol, ↓ in inhibitory neurotransmitter GABA results in unopposed sympathetic activity. DT occurs in 5% with alcohol withdrawal.

Clinical features

- Withdrawal symptoms may develop <8h following last drink (usually peak at 48–72h), and consist of confusion, hallucinations (auditory, visual, olfactory or formication), agitation, insomnia, nausea, and vomiting. Generalized seizures may occur. Signs of sympathetic drive include ↑ HR, ↑ BP, sweating, tremor, dilated pupils, and fever.
- Delirium tremens signs and symptoms include all of these points, but with greater severity. Neuropsychiatric manifestations (particularly visual hallucinations) prominent. Mortality >20% untreated; 5% with treatment. Death often due to complications of hyperthermia, electrolyte imbalance, volume depletion, infection, hypertensive crisis, or cardiovascular collapse.

Diagnosis

Largely clinical diagnosis. Always consider in any recently admitted agitated and confused patient (see ▶ Approach to agitation and confusion in the GI patient). Important differential diagnoses include drug intoxication (alcohol or other drugs), ➲ Wernicke encephalopathy, Korsakoff syndrome, ▲ **hepatic encephalopathy** ▲, or intracranial haematoma.

Investigation

- Bloods:
  - FBC: ↑ WCC, ↑ MCV, ↓ platelets may be seen.
  - ↑ PT/APTT suggests significantly impaired liver function.
  - U&E, LFTs: dehydration common; abnormal LFTs not prerequisite for alcohol withdrawal; hypomagnesaemia common.
  - Glucose: seizures may occur secondary to hypoglycaemia.
  - Detectable alcohol during ‘withdrawal’ suggests alternative diagnosis.
- ECG: excludes other causes of tachycardia (e.g. AF common).
- CT brain: in patients with history of head injury, atypical presentation, focal neurology, or prolonged post-ictal phase.
- CXR and cultures (e.g. blood, urine, sputum, ascites if present) if signs of sepsis.

Management

- Manage patient in calm, safe environment. Monitor vital signs (HR, BP, temperature).
- Peripheral IV cannula. Give fluids and thiamine supplementation (Pabrinex® IV 2 pairs tds for 3d followed by thiamine 100mg PO bd).
- Benzodiazepines of proven benefit (e.g. lorazepam 1mg = diazepam 5mg = chlordiazepoxide 25mg), but no universally agreed protocol. Shorter-acting lorazepam favoured in liver disease (as less dependent on hepatic metabolism), and midazolam increasingly being used.
- Mild to moderate alcohol withdrawal:
  - ‘Symptom-triggered’ regimens (e.g. chlordiazepoxide 20–100mg PO every 2h until symptoms controlled, then prn) give better control and shorter treatment duration than ‘fixed schedules’.
  - ‘Fixed-schedule’ regimen. Dosing should be based on severity as measured using CIWA-Ar score 🖱 http://www.mdcalc.com/ciwa-ar-for-alcohol-withdrawal/ or equivalent (Table 4.4).[6]
- Severe withdrawal/DT:
  - Lorazepam 1–4mg IV every 1–3h (interval dosing). Onset of action occurs 2–5min after IV injection, but peak plasma levels at 1–6h. Close monitoring for respiratory depression essential. Adjust dosage and frequency to patient response (aim for calm, but awake). Dosage not to exceed 240mg/24h.
  - Haloperidol can be given in addition if severely agitated. Dose 3mg IV, with doubling of successive doses every 30min until calm.
- Other drugs for withdrawal (e.g. barbiturates, propofol, carbamazepine, clonidine) should not be used as 1st line therapy.

Table 4.4 ‘Fixed-schedule’ chlordiazepoxide oral regimen for alcohol withdrawal

Severity	Day 1	Day 2	Day 3	Day 4	Day 5
Mild	20mg qds	10mg qds	5mg qds	5mg bd	
Moderate	30mg qds	20mg qds	10mg qds	5mg qds	5mg bd
Severe	40mg qds	30mg qds	20mg qds	10mg qds	5mg bd

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[6] Sullivan JT *et al.* (1989). *Br J Addict* **84**: 1353–7.

Alpha-1-antitrypsin (α1AT) deficiency

Genetic condition with autosomal co-dominant inheritance. Associated with pulmonary, liver, and skin disease. Normal levels of α1AT seen in patients who carry the common (M) allele of *α1AT* gene, while Z allele is most deficient variant. Hepatic disease occurs due to polymerization and accumulation of Z variant in hepatocytes.

Clinical features

- PiZZ phenotype associated with lung disease (panacinar emphysema).
- Neonatal cholestasis and jaundice develop in 10% of homozygotes, with subsequent hepatomegaly and portal hypertension. LFTs show ↑ cholestatic enzymes and transaminases. Presentation in adulthood occurs in 10% of homozygotes, with cirrhosis or emphysema (rarely both in same patient). High rates of ➲ portal hypertension and ➲ hepatocellular carcinoma.

Investigations

Diagnosis made by finding serum α1AT level <75% lower limit of normal (80mg/dl), α_1-globulin level on protein electrophoresis, genetic phenotyping by immunofixation, and PAS-positive globules in peri-portal hepatocytes on histology.

Management

- No specific therapy. Prevent hepatic insults (e.g. avoid alcohol excess, vaccinate against HAV/HBV), ensure adequate nutrition, and avoid smoking.
- → Ursodeoxycholic acid may help with neonatal cholestasis.
- ➲ Liver transplantation remains only treatment for advanced disease, with 80% 5y survival in children.
- Inhaled α_1-antitrypsin has been used to treat pulmonary disease, but ineffective for liver manifestations (as not due to ↓ enzyme activity).

Alpha chain disease

Also known as immunoproliferative small intestinal disease (IPSID). It is a disorder of B lymphocytes involving proliferation of lamina propria plasma cells in upper small intestine and associated mesenteric lymph nodes, seen in Mediterranean countries, South America, and the Far East. It usually affects lower socioeconomic groups in areas with poor hygiene and high incidence of bacterial and parasitic GI infection. Plasma cells produce truncated monoclonal heavy chains that lack associated light chains. Presents with malabsorption and diffuse lymphoid infiltration of small bowel. Diagnosis made by detecting α chains in serum. Initial response to antibiotics (tetracyclines), but late-stage disease characterized by lymphoma.

Alpha-fetoprotein (αFP)

See ➢ CPD p. 148.

Aminosalicylates

See: → 5-AMINOSALICYLATES (5-ASA) preparations.

Amoebiasis

Epidemiology and pathology

Entamoeba histolytica pathogenic in humans and causes amoebic colitis and ➔ liver abscess (ALA). Two-stage life cycle of infectious cyst then motile trophozoite. Cysts can live outside hosts or be carried asymptomatically in stool, while trophozoites (passed by people with invasive disease) cannot survive outside host. Acquisition faeco-oral.

Clinical features

Varies from asymptomatic, to life-threatening colitis. Typically presents with bloody diarrhoea (multiple, small volume, mucoid stools), abdominal pain, and tenderness. Tenesmus in >90%. Misdiagnosis as ➔ ulcerative colitis and treatment with → CORTICOSTEROIDS may predispose to perforation and sepsis. Systemic dissemination may occur.

- Colonoscopic appearance of shallow ulcers, most common in right colon. Ulcers may erode into blood vessels or cause intestinal perforation and peritonitis.
- ALA in 1–4% following haematogenous spread via portal vein, with ♂ predominance (despite equal sex distribution for colitis). Clinical features: abdominal pain (chest wall, shoulder tip or scapula pain if laterally sited or subdiaphragmatic), fever (often in spikes), and constitutional symptoms. Jaundice in <15%.
- Colonic narrowing may be due to amoeboma (managed medically, because surgical resection has high complication rate).
- Respiratory tract involvement includes atelectasis and transudative pleural effusion (common, especially right-sided); these do not require specific treatment. Patients developing cough, pleuritic chest pain, and respiratory distress could have pleuropulmonary amoebiasis secondary to ALA rupture through diaphragm. If hepatobronchial fistula develops, patients produce copious amounts of brown sputum containing necrotic material and occasional trophozoites.

Investigation

- Diagnosis involves careful stool microscopy to look for cysts or trophozoites. At least 3 samples within 10d ↑ detection to 85–95%:
  - Presence of haemophagocytic trophozoites (intracytoplasmic RBCs) on 'hot stool', sent to lab within 15min, pathognomonic.
  - Otherwise cysts are morphologically indistinguishable from non-pathogenic *Entamoeba dispar* or *coli*. Subsequent antigen detection tests help differentiate.
- Usually few leucocytes in the stool.
- Sigmoidoscopy can help, but rectal involvement less frequent than caecal, so colonoscopy is investigation of choice. Commonly see scattered ulcers with basal slough on otherwise normal mucosa.

- Plain AXR if severe abdominal pain and systemic upset to exclude toxic ➲ megacolon.
- Liver abscess identified on US or CT. Routine aspiration not indicated for diagnostic purposes, but if pus is evacuated it has a characteristic brown 'anchovy sauce' appearance.
- Serum enzyme immunoassay (EIA) 99% sensitive and 90% specific in ALA; sensitivity 66% in colonic amoebiasis.

Management

- Colitis: → METRONIDAZOLE 400mg PO tds for 5–10d or tinidazole 2g daily for 3d (better tolerated, fewer treatment failures).
- ALA: → METRONIDAZOLE 800mg PO tds for 7d or tinidazole 2g daily for 5d. Cure in 90%. Therapeutic needle aspiration/catheter drainage only considered if:
  - Abscess >5cm and ∴ at risk of rupture.
  - Left lobe ALA (↑ risk of intraperitoneal/pericardial rupture).
  - Failure to gain clinical response to therapy within 1wk.
- Always follow treatment with 2nd drug to eliminate luminal cyst carriage. Paromomycin 500mg PO tds more effective than diloxanide 500mg PO tds. Treat for 10d.[7]
- Asymptomatic cyst carriage common in endemic areas. Role of treatment debated as complications infrequent and reacquisition high. Case for treatment in non-endemic settings as less likely to recur and putative role in disease prevention.[8]

Ampullary cancer

- Rare (<0.5% of GI cancers). May present with painless obstructive jaundice. Usually develops from ampullary adenoma, often in association with ➲ familial adenomatous polyposis (FAP; 3–12% ampullary cancer risk, surveillance required), although can occur spontaneously. Average age of presentation 60–70y, unless part of FAP.
- Abnormal ulcerated ampulla at ERCP. Dilated pancreatic and common bile ducts (➲ double-duct sign) may mimic ➲ pancreatic cancer. CT scan ± EUS to define local invasion.
- Prognosis depends on histomolecular phenotype, with pancreatobiliary phenotype having worse outcome than intestinal phenotype.
- Approximately 50% resectable, with >80% 5y survival following ➢ Whipple's resection in those without local invasion (i.e. much better than for ➲ pancreatic cancer). Non-operative cases treated with endoscopic biliary stenting ± palliative chemotherapy.

Amylase

See ➢ CPD p. 147.

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[7] Wright SG (2012). *Infect Dis Clin North Am* **26**: 323–39.

[8] Blessmann J & Tannich E (2002). *N Engl J Med* **347**: 1384.

Amyloidosis

Group of diseases characterized by extracellular deposition of abnormal fibrillar proteins. Classification is by capital 'A' for amyloid followed by an abbreviation for the fibril protein.

- **Light chain (AL) amyloidosis** involves clonal excess of immunoglobulin light chains (e.g. by multiple myeloma). Tends to infiltrate muscularis propria. GI manifestations include macroglossia, gastroesophageal reflux, bleeding, and motility problems (including ➲ pseudo-obstruction). Treatment symptomatic, and of underlying haematological cause with cytotoxic chemotherapy.[9]
- In **reactive systemic (AA) amyloid**, precursor protein is acute phase reactant serum amyloid A. Occurs in <1% of patients with ➲ Crohn's disease and 0.07% with ➲ ulcerative colitis. Presentation usually with nephrotic syndrome but diarrhoea, malabsorption, and hepatosplenomegaly may develop. Treatment symptomatic, and of underlying cause.
- **Hereditary systemic amyloidoses** are autosomal dominant disorders, most common causes of which are mutations in transthyretin (ATTR) or lysozyme (ALys) gene.
    - In **ATTR amyloid**, fibrils deposit in myenteric plexus more than with other types of amyloid. An siRNA-based therapy directed at reversing underlying pathology has shown promise in Phase I clinical trial, which may open up novel avenue for treatment of other types of amyloidosis.[10]
    - **ALys amyloid** is a non-neuropathic disorder that mimics AL amyloid, predominantly affecting the GI tract, liver, and kidneys.
- ➲ Familial Mediterranean fever also involves AA protein; in this disease colchicine prevents renal failure from amyloid deposition.
- Gastroenterologists sometimes called to help make diagnosis of amyloid. Rectal and duodenal biopsies positive in >80% of cases if submucosa present in biopsy. Show 'apple green' birefringence with Congo red staining. Nuclear scintigraphy for serum amyloid P component also available.

Anal cancer

Epidemiology and pathogenesis

Rare (incidence 1/100,000/y). Comprise 1–2% of lower GI cancers. Risk factors include genital warts and receptive anal sex. Human papilloma virus types 16 and 18 associated with squamous tumours.

Clinical features

Mean age at presentation: 60y. Usually presents with bleeding, pain, and pruritus, but 25% of patients asymptomatic.

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[9] Cowan AJ *et al*. (2013). *Haematologica* **98**: 141–6.

[10] Coelho T *et al*. (2013). *N Engl J Med* **369**: 819–29.

Management

- Adenocarcinomas of anal canal behave like those of rectum. Treated in similar way, with abdominoperineal resection and pre- or postoperative chemoradiation for large or invasive tumours.
- 80% of cancers are squamous cell cancers, and for this group chemoradiotherapy has replaced aggressive surgery, resulting in improved 5y survival of 70%.
- Non-epidermal tumours very rare. Include melanomas, intraepithelial neoplasia (Bowen's disease), and intraepithelial mucinous adenocarcinoma arising from apocrine sweat glands (Paget's disease).

Anal fissure

Epidemiology and pathology

Painful linear ulcers in anal canal. Young and middle-aged adults most commonly affected (♂=♀). 90% of primary fissures in posterior midline. Can also be secondary to ➔ Crohn's disease, anal cancer, and infection (syphilis, ➔ tuberculosis), in which case usually more lateral.

Elliptical arrangement of fibres of anal sphincter supposed to offer less muscular support to mucosa posteriorly, predisposing to traumatic tears after passage of large hard stool. Repeated trauma can lead to chronic fissures. In these patients, resting anal tone high (although cause or effect unclear) and may produce degree of ischaemia that can lead to fibrosis.

Clinical features

Severe sharp pain during and after defaecation, with scanty bright red bleeding. Digital examination or proctoscopy usually too painful without topical anaesthesia. Simple inspection may reveal diagnosis. Sentinel pile (fibrotic nubbin of skin at anal verge) common.

Treatment

- Stools must be made soft and easy to pass (ensure high oral fluid intact; use non-stimulant osmotic → LAXATIVE).
- Topical anaesthetics and frequent baths can ↓ sphincter spasm.
- Medical treatment with topical nitrates or diltiazem effective at ↑ fissure healing.
- Surgical therapy includes sphincterotomy, which ↓ sphincter tone. Lateral sphincterotomy has better results than midline + fistulectomy.
- Manual dilatation under anaesthesia produces very uncontrolled results, frequent complications, and is now discredited.

Anaphylaxis

IgE-mediated hypersensitivity to foods. May be localized to oropharynx (oral allergy syndrome), with pruritus, angioedema of tongue, lips, palate, and throat; or generalized with skin and airway involvement, and cardiovascular collapse. Symptoms develop min to 2h after eating, with nausea, vomiting, abdominal pain, diarrhoea.

Diagnosis

- Established by history and food-specific IgE antibodies.
- Serial measurement of plasma mast cell tryptase helpful if uncertainty and generalized symptoms.
- Oral food challenge rarely required, and should only be performed with caution (in an environment with appropriate staff and equipment to rapidly manage further attack). Can occasionally be useful in confirming diagnosis.

Treatment

- Antihistamine (e.g. chlorphenamine 10mg IV) and steroid (hydrocortisone 200mg IV).
- IV fluids and adrenaline 0.5mg IM if hypotension or stridor, repeated if necessary.
- To prevent recurrence, strict elimination of offending allergen with scrutiny of food labels only proven therapy.

Angiodysplasia (see Plate 18)

Gastrointestinal mucosal vascular ectasia is most commonly found in patients >60y. Identified in 1–2% undergoing upper GI endoscopy for any indication, 4% if being endoscoped for bleeding (more if being investigated for anaemia), and 3–6% in those undergoing colonoscopy.

Aetiology

May be degenerative, relating to chronic low-grade mucosal vein obstruction or mucosal ischaemia. Much quoted (and debated) association with aortic valve disease (Heyde syndrome), potentially linked to acquired form of von Willebrand disease.

Clinical features

Primarily from loss of blood through GI tract, which can range from haematemesis to PR bleeding to occult anaemia. Not life-threatening in majority, but 15% of patients with colonic angiodysplasia have acute massive haemorrhage.

Investigation

Diagnosis usually endoscopic (see Plate 18). Lesions may be indistinguishable from those of ➲ hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu syndrome), Turner's syndrome, and CREST syndrome (see ➲ systemic sclerosis), although extraintestinal signs of these disorders not seen. Angiodysplasia of small intestine can be diagnosed by push enteroscopy or ➲ video capsule endoscopy. Colonic lesions diagnosed at colonoscopy or angiography.

Management

Most often with endoscopic obliteration procedures, such as ➢ argon plasma coagulation; rebleeding rate substantial. In patients unfit for surgery, transcatheter embolization using coils or Gelfoam® is successful in stopping acute bleeding. Surgery may be definitive treatment if bleeding source clearly defined. Medical treatment with oestrogen–progestogen (0.05mg ethinylestradiol and 1mg norethisterone daily) has been tried in hope of optimizing coagulation, microvascular circulation, or endothelial integrity, but efficacy not fully established.

Anorectal abscesses

Aetiology and pathogenesis

Usually result from infection of anal glands along dentate line. Acute infection may cause abscess and lead to chronic anorectal fistula. Abscesses classified according to where they extend to, and may be perianal, ischiorectal, intersphincteric, or supralevator (Fig. 4.2). Most common is perianal (40–50%), and least common are supralevator (5–10%).

Diagnosis

Can be difficult because there may be no external signs and rectal examination may be painful. Examination under anaesthetic, MRI, or intra-anal US can all be very helpful.

Treatment

- Requires incision and drainage.
- Culture of pus not usually necessary.
- Antibiotics alone inadequate, although → METRONIDAZOLE and → CIPROFLOXACIN have important adjunctive roles.
- IV antibiotics may be needed if patient immunocompromised, diabetic, or shows signs of systemic sepsis.

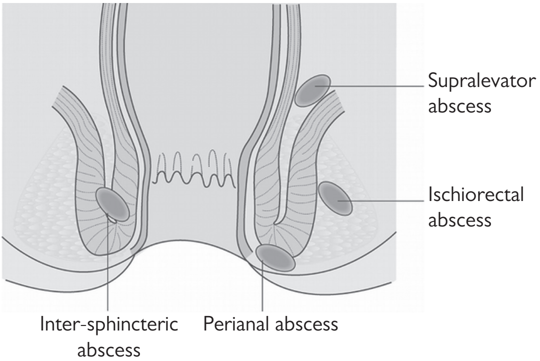

Fig. 4.2 Classification of anorectal abscesses.

Anorectal fistulae

Complication of perianal abscess, resulting in connection between anorectum and skin at anal verge or elsewhere in perineum. Any discharging area or area of granulation around anus should be assumed to connect with anorectum until proven otherwise. **Goodsall's rule** states that for anorectal fistulae where the external opening lies anterior to the transverse anal line, the internal opening is usually at the nearest point in the anal canal; for those where the external opening is posterior, the internal opening is usually in midline. Most surgeons will use operative exploration as their 1st diagnostic test for fistula, but MRI very useful in defining complex or recurrent fistulae. External and internal openings must be defined, and presence of any extensions established. An underlying disease process such as ➲ Crohn's disease, ongoing infection, or presence of a foreign body, must not be missed. Biopsy often needed.

Classification is by relation to internal and external sphincters. Four major categories: intersphincteric, trans-sphincteric, extrasphincteric, and suprasphincteric (Fig. 4.3).

Preoperative assessment of sphincter function by anorectal manometry and anorectal US is wise when any degree of sphincter damage is anticipated. Only those tracks passing through distal parts of the sphincter can be laid open without fear of incontinence. For fistulae not amenable to fistulotomy, insertion of ➲ seton suture is a safer option than cutting and repairing the sphincter, which often does not heal well. Complex or high fistulae require complex surgery.

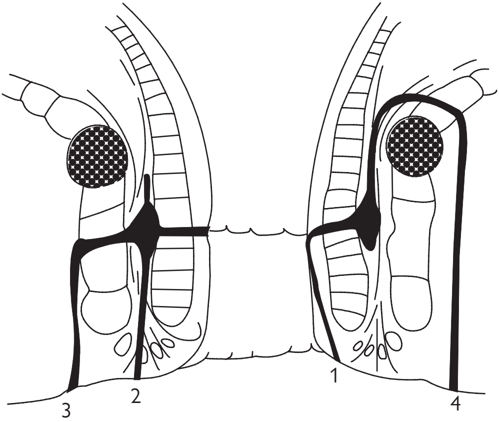

Fig. 4.3 Classification of anorectal fistulae: (1) superficial; (2) intersphincteric; (3) trans-sphincteric; (4) suprasphincteric.

Anorectal manometry

See: ⊳ 'manometry' (p. 450).

Anorexia nervosa

Eating disorder characterized by distorted body image, ↓ ➲ body mass index, inability to interpret hunger and satiety, and pathological pursuit of thinness. See also ► Approach to eating disorders and ➲ bulimia.

Aetiology and pathogenesis

Not a true loss of appetite, but preoccupation with food and eating. Incidence 30–150/100,000 ♀ aged 16–25y, making it 3rd most common illness in this age group after obesity and asthma. Role of psychosocial factors much studied and beyond the scope of this text.

Clinical features

Hypothermia; bradycardia; hypotension; acrocyanosis; carotenaemia (giving yellow appearance to face and hair); thin hair (lanugo) over face, arms, and back; and amenorrhoea.

Investigation

May reveal hypokalaemia, hyponatraemia, 'sick euthyroid' indices (↓ free thyroxine with normal TSH), hypoglycaemia, and ↓ WCC.

Complications

- Arrhythmias, prolonged QT.
- Osteopaenia/➲ osteoporosis.
- Depressed menstruation and subfertility.
- GI complications include:
  - ➲ Constipation.
  - ➲ Pancreatitis.
  - ➲ Oesophagitis.
  - ➲ Peptic ulceration.
  - Abnormal ⊳ liver function tests.
  - Malabsorption.
  - Reduced taste.

Treatment

Difficult, and centres on interlocking approach to psychological, nutritional, and medical problems. Usually best managed by a Specialist Eating Disorders Unit (SEDU), though see ► Approach to eating disorders for guide as to who should be admitted to medical bed, and treatment of acute medical complications. Sadly, while early mortality remains ≈5%, late mortality can be as high as 20%, with suicide, arrhythmias, and infections as the leading causes of death.

Antibiotic-associated diarrhoea (AAD)

Common: occurs after 5–25% of antibiotic courses. Two main forms:

- Idiopathic, with no known pathogen (90%). Onset during antibiotic exposure, dose-related frequency, resolves when antibiotic discontinued, no inflammation on colonic biopsy or stool examination for leucocytes, and benign course.
- Diarrhoea associated with *Clostridioides difficile* (≈10%). See ➲ clostridial infections of GI tract.

Mechanisms

- Direct effects of antibiotics on intestinal mucosa (e.g. neomycin and clofazimine; erythromycin prokinetic through motilin receptor).
- Effects on gut ecology through altered bile acid metabolism and carbohydrate fermentation, as well as overgrowth of pathogens.

Management

- Meta-analyses show benefit of probiotic administration with lactobacillus or saccharomyces.
- Often responds rapidly to cessation.
- See also ➲ clostridial infections of GI tract and ► Approach to acute diarrhoea.

Aorto-enteric fistulae

Nearly always occur after reconstructive aorto-iliac surgery. Frequency ≈1/200 patients, at an average of 3–5y after operation. Usually affects 3rd part of duodenum, so out of reach of standard upper GI endoscopy. Diagnosis requires enteroscopy or CT angiography. ❗ Always suspect diagnosis if any hint of upper GI bleed in patient with appropriate surgical history: there is classically a self-limiting 'herald bleed', which may be the only chance to save patient's life, since this is often followed by a 2nd massive life-threatening bleed.

Pathogenesis usually subtle infection with *S. aureus* or *E. coli*, so beware of low-grade fever, unexplained fatigue, raised inflammatory markers, or leukocytosis in appropriate clinical setting. Management requires immediate involvement of vascular surgeons, for emergency laparotomy or endovascular stenting.

Aphthous ulcers

See: ➲ mouth ulcers.

Appendix and appendicitis

Acute appendicitis remains the most common surgical emergency and may involve gangrene or perforation into the abdominal cavity. Management is surgical appendicectomy (medical treatment with antibiotics alone inferior). See ▲ **acute abdominal pain** ▲. Although function of appendix remains speculative, high concentration of lymphoid tissue has always suggested immune regulatory function. Epidemiological data show appendicectomy has protective effect in ➲ ulcerative colitis and ➲ Crohn's disease.[11]

Ascites

See: ▶ Approach to ascites.

Autoimmune hepatitis (AIH)

Aetiology and epidemiology

Necro-inflammatory liver disease of unknown aetiology. Estimated prevalence: 50–100 cases/million population (♀:♂ ratio 4:1). Strongly associated with HLA alleles DR3 (often younger at onset, more severe course) and DR4 (older, more benign course).

Clinical features

- Bimodal age distribution at onset: 10–30y and >40y. Young ♀ commonly affected, but found in all other groups.
- Acute hepatitis in up to 40%, but ▲ **acute liver failure** ▲ very rare. Many present with gradual onset of jaundice, fatigue, abdominal pain, and fever; 30–80% have cirrhosis at presentation.
- Associated with other autoimmune diseases in 48%: thyroid disease, arthritis, vitiligo, ➲ ulcerative colitis, diabetes mellitus, lichen planus, alopecia, mixed connective tissue disease.
- Prior to immunosuppression, 50% 3–5y mortality reported. When remission induced, 90% 10y survival, even with cirrhosis at outset.
- Overlap syndromes may occur. In presence of clinical features of AIH, antimitochondrial Abs (AMA) and ➲ cholangitis seen in 8%, suggesting overlap with ➲ primary biliary cholangitis (PBC), and biliary disease suggestive of ➲ primary sclerosing cholangitis (PSC) in 6%.
- Anti-LKM1 Abs found in 2–5% of patients with ➲ hepatitis C.

Investigations

- Definitive diagnosis requires circulating autoantibodies >1:80 titre, IgG >1× ULN, and other causes of chronic liver disease excluded. Characteristic elevation of transaminases (ALT/AST) by >1.5× ULN for >6mo. ALT >1,000U/L rarely seen.
- Three subtypes of AIH categorized:

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[11] Parian A *et al*. (2017). *Gut* **66**: 1390–7.

  - **Type 1 (classical):** 80% of cases. 70% ♀, <40y. ANA ± smooth muscle Ab (ASM) +ve. ↑ IgG in 97%. Good response to immunosuppression in 80%, but 25% cirrhotic at presentation.
  - **Type 2** Very rare. Accounts for <10% of cases in Europe. Usually diagnosed in children. Associated with anti-liver–kidney microsomal Abs (anti-LKM1) and anti-liver cytosol antigen (ALC-1) Abs, but ANA/ASM usually negative. Rapidly progressive, and poor response to immunosuppression.
  - Incorporation of clinical, laboratory and histological parameters into standardized scoring systems may aid diagnosis where classical features absent (simplified diagnostic criteria for the diagnosis of AIH, see Box 4.5).
- ➲ Liver biopsy. Periportal/lobular lymphoplasmacytic hepatitis characteristic, but no pathognomonic features. Histological grade (inflammation) and stage (fibrosis) predict prognosis (bridging necrosis/multilobular necrosis/cirrhosis probably predict worse outcome). Repeat biopsy on-treatment predicts likelihood of maintained remission off-treatment.

Box 4.5 Simplified diagnostic criteria for AIH

Feature/parameter	Discriminator	Score
ANA or SMA+	≥1:40	+1*
ANA or SMA+	≥1:80	+2*
or LKM+	≥1:40	
or SLA+	Any titre	
IgG	> ULN	+1
or Ig levels	> 1.1 × ULN	+2
Liver histology	Compatible with AIH	+1
	Typical of AIH	+2
Absence of viral hepatitis	No	0
	Yes	+2

≥6 = probable AIH
≥7 = definite AIH

* addition of points achieved for all antibodies (maximum 2 points only)

Management

Treatment indicated when ALT/AST >1.5× ULN, IgG >2× ULN, and moderate to severe periportal hepatitis on biopsy. Absolute indication if ALT/AST >10× ULN, severe hepatitis and necrosis, or disease progression.

- → CORTICOSTEROIDS. Mainstay of treatment, with 80% biochemical and histological remission within 2–4y. Initiated alone, or with → AZATHIOPRINE. Usual starting dose prednisolone 30–50mg od PO for 2wk, with aim of reduction of 5mg every 10d to maintenance at 5–15mg/d. Drug withdrawal should not be attempted <2y after starting treatment, and then guided by histology (100% relapse if on-treatment progression to cirrhosis; 20% if histological resolution). Disease flares may occur whatever the response. Progression in 10% despite steroids.
- Budesonide (9mg/d, taper over 6–18wk) can be used in non-cirrhotic patients.

- → AZATHIOPRINE. No role as monotherapy for inducing remission. Very useful in combination with steroids, allowing steroid reduction, and as maintenance therapy after steroid withdrawal (maintains remission in >80% over 1–10y follow-up). Usual dose 1–1.5mg/kg/d in combination, increasing to 2–2.5mg/kg/d as monotherapy after remission achieved. Important side effects (see → Section 4, p. 614), and checking ➲ TPMT levels prior to commencing treatment essential.
- Other immunosuppressants. Effectiveness of → TACROLIMUS (aim: trough of 6–10ng/ml), → CICLOSPORIN (aim: trough of 150–250 ng/ml), mycophenolate mofetil (1g bd), and others reported (e.g. → anti-TNF, rituximab, but little data). Can be considered for treatment failures.
- ➲ Liver transplantation. Consider in progressive disease, especially if no response after 4y of treatment or early hepatic decompensation. 5y and 10y survival post-transplant 90% and 75%, respectively. AIH recurs in 20% of grafts, but rarely leads to graft loss.
- Patients with cirrhosis should undergo HCC surveillance.
- DEXA scan every 2–5y (more regularly if long-term steroids).

Guideline

BSG guidelines for management of AIH (2011). 🖱 https://www.bsg.org.uk/resource/bsg-guidelines-for-the-management-of-autoimmune-hepatitis.html.

Autoimmune pancreatitis (AIP)

Autoimmune pancreatitis (AIP) may be a primary pancreatic disorder, or occur in association with other immune disorders, including IgG4-related disease, mediastinal/retroperitoneal fibrosis, and ➲ inflammatory bowel disease.

Clinical features

Manifestations include:

- Pancreatic mass (may be mistaken for carcinoma or lymphoma).
- Abdominal pain ± ➲ acute or ➲ chronic pancreatitis.
- Biliary and pancreatic ductal strictures, causing obstructive jaundice.

Diagnosis

Usually requires pancreatic biopsy. Diffusely enlarged pancreas with featureless borders on CT or MRI highly suggestive.

- **Type 1 AIP** Pancreas involved as part of systemic IgG4-related disease, and meets HISORt criteria (Table 4.5).
- **Type 2 AIP** Characterized by granulocytic lesions without IgG4$^+$ cells. Lower likelihood of systemic involvement and relapse.

Treatment

- Good response to → CORTICOSTEROIDS (e.g. prednisolone 30mg od, reducing by 5mg every 2wk).
- Up to 40% relapse after initial treatment course (more likely if high serum IgG4), necessitating immunosuppression with → AZATHIOPRINE.

Table 4.5 HISORt criteria for Type 1 autoimmune pancreatitis/IgG4-related pancreatitis

Category	Criteria
Histology	At least 1 of: Periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis. Lymphoplasmacytic infiltrate with >10 IgG4+ plasma cells/higher power field.
Pancreatic **I**maging	Typical: diffuse gland enlargement; diffuse attenuated pancreatic duct. Others: focal mass/stricture; atrophy; calcification; pancreatitis.
Serology	↑ serum IgG4.
Other organs	Hilar/intrahepatic strictures; persistent biliary stricture; parotid/lacrimal gland; mediastinal lymphadenopathy; retroperitoneal fibrosis.
Response to steroid **t**reatment	Resolution/marked improvement of pancreatic/extrapancreatic manifestation.

Autonomic neuropathy

Aetiology

Autonomic neuropathy affecting GI tract occurs as complication of ➲ diabetes mellitus and ➲ Parkinson's disease. Less common causes include ➲ amyloidosis, ➲ Fabry's disease, and ➲ porphyria.

Clinical features

Commonest symptoms relate to postural hypotension and genitourinary involvement (impotence, loss of morning erections, urinary urgency). Gut stasis can give rise to ➲ bacterial overgrowth, which can produce diarrhoea and malabsorption. Nausea, vomiting, abdominal pain, and distension can all occur as presenting problems.

Examination

In GI system, test for succussion splash suggestive of gastroparesis, and look for faecal impaction.

Investigations

- Autonomic function tests may help (refer to specialist unit).
- Endoscopy is a poor test for motility: better to get video swallow, barium meal, or gastric emptying study. Colonic motility can be assessed using a shapes test, where clearance of differently shaped radio-opaque markers assessed on sequential plain AXRs.

Treatment

Small frequent meals and avoidance of anticholinergics, narcotics, and sympathomimetics. → PROKINETICS may provide benefit (e.g. erythromycin, metoclopramide).

B

Bacterial overgrowth *254*
Balloon dilatation: see ▷ ‘Endoscopic dilatation’ (p. 216) *255*
Barrett’s oesophagus *255*
Barrett’s surveillance: see also ▷‘Surveillance’ (p. 169) *257*
Behçet’s disease *258*
Beriberi *259*
Bezoars *259*
Bile acid malabsorption *260*
Biliary atresia *261*
Biliary bypass procedures: see ▷ ‘Biliary bypass procedures’ (p. 185) *261*
Biliary colic: see ➲ Choledocholithiasis *261*
Biliary reflux *262*
Biliary strictures *262*
Bilharzia: see ➲ Schistosomiasis *263*
Biofeedback *263*
Blastocystis *263*
Blatchford score: *see* ➲ Scoring systems for predicting outcomes in GI bleeds *264*
Body mass index (BMI) *264*
Boerhaave syndrome *264*
Botulism *265*
Bougies *265*
Breath tests: see ▷ ‘Breath tests’ (p. 152) *265*
Budd–Chiari syndrome (BCS) *266*
Bulimia *267*
B vitamins: see ➲ vitamins *267*

Bacterial overgrowth

Refers to ↑ in the normally low bacterial colonization of GI tract upstream of distal ileum. Causes bloating, diarrhoea, and abdominal pain, and occasionally malabsorption, malnutrition, and weight loss.

Aetiology and pathophysiology

Contributing factors shown in Box 4.6.

- Fat, protein, carbohydrate, and vitamin malabsorption result from poor enterocyte function and bacterial transformation of nutrients into non-absorbable and toxic metabolites.
- Anaerobes deconjugate bile acids, preventing bile acid function and enterohepatic circulation. Deconjugated bile acids induce watery diarrhoea.
- Carbohydrate intolerance results from reduction of brush border disaccharidases. Increased amounts of osmotically active carbohydrate fragments contribute to diarrhoea.
- Anaerobes compete with host for vitamin B_{12}, resulting in deficiency and macrocytic anaemia.

Clinical features

Diarrhoea, weight loss, neurological features if significant ➲ vitamin B_{12} deficiency, abdominal pain, and symptoms of impaired absorption of fat-soluble ➲ vitamins A, ➲ D, ➲ E, and ➲ K.

Investigation

Microbiological culture most direct method (>10^5 colonies/ml after duodenal aspiration and culture), but rarely used in clinical practice. Hydrogen breath testing after glucose oral load (see ➢ 'Breath tests', p. 152) less invasive. ➢ SeHCAT test useful for identifying ➲ bile acid malabsorption. Also see ▶ Approach to malabsorption and steatorrhoea.

Treatment

If surgical correction of underlying abnormality leading to stasis is not possible, antibiotics and treatment of dysmotility are mainstays of therapy. Antibiotic regimens usually empirical and involve drugs with activity against aerobic and anaerobic bacteria. Tetracycline 250mg qds is traditional choice, with rifaximin the most studied to date. Co-amoxiclav, amoxicillin, co-trimoxazole, and ciprofloxacin are alternatives. Often a single 14d course can relieve symptoms for months, but sometimes continuous rotating combinations are necessary. So far, trials of probiotic therapy are negative or inconclusive.

Box 4.6 Causes of bacterial overgrowth

Reduced host defences

- Hypogammaglobulinaemia.
- Immunodeficiency (e.g. ➲ HIV).
- Old age.
- ➲ Chronic pancreatitis.

Excess bacterial entry to small bowel

- Atrophic gastritis/gastric acid suppression (e.g. PPIs).
- Gastro-jejunostomy/Roux-en-Y anastomosis (see ➢ p. 185).
- Gastrectomy (see ➢ p. 183).
- Enteral fistulae.

Delayed small bowel clearance

- Small bowel/➲ jejunal diverticula (e.g. ➲ scleroderma).
- Strictures (e.g. ➲ Crohn's disease, post-surgical).
- ➲ Pseudo-obstruction.
- ➲ Amyloidosis.
- ➲ Autonomic neuropathy (e.g. ➲ diabetes, post-vagotomy).

Balloon dilatation

See: ➢ 'Endoscopic dilatation' (p. 193).

Barrett's oesophagus

Named after Norman Barrett, British surgeon (died 1979), although condition first described by P.R. Allison in 1948.

Definition

Metaplastic columnar epithelium lining lower oesophagus, clearly visible endoscopically, >1cm above gastroesophageal junction and confirmed with histology (Plate 9).

Pathogenesis and epidemiology

Usually arises as adaptive change to reflux oesophagitis. Columnar mucosa more resistant to acid than squamous, but the price for protection is high, as can become metaplastic and pre-malignant. Incidence of developing adenocarcinoma from Barrett's oesophagus 30-fold that of general population, although this equates to annual risk of 0.1–0.5%.[1, 2]

Clinical features

Asymptomatic, or associated with symptoms of ➲ oesophagitis.

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[1] Hvid-Jensen F *et al.* (2011). *N Engl J Med* **365**: 1375–83.

[2] Bhat S *et al.* (2011). *J Natl Cancer Inst* **103**: 1049–57.

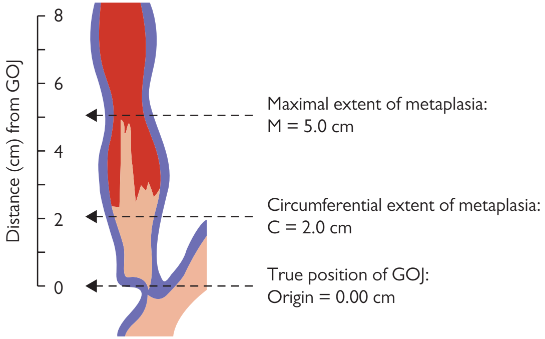

Fig. 4.4 Barrett's oesophagus Prague classification.

Reproduced with permission from ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus, *American Journal of Gastroenterology* 111(1):30–50, January 2016.

Box 4.7 Practice point: diagnosis of Barrett's oesophagus

Correct endoscopic identification of anatomical landmarks vital (also affects interpretation of histology). Diagnosis often imprecise because of failure to document (see Fig. 4.4):

- Level of diaphragmatic crus (usually 40cm in ♂and 38cm in ♀) and identification of hiatus hernia if present.
- Gastro-oesophageal junction where gastric rugal folds peter out into tubular oesophagus (the 'sphincter pinch').
- Squamocolumnar junction.

All endoscopy reports should include these values if there is any question of Barrett's oesophagus. See 'Classification', next.

Diagnosis

Requires oesophageal biopsies showing columnar epithelium (Box 4.7). Endoscopy alone not sufficient. In general, risk of malignancy seems to be associated with presence of intestinal metaplasia on biopsy. ⓘ Do not confuse Barrett's oesophagus with cervical inlet patch of columnar mucosa in upper oesophagus. This is usually congenital, may cause symptoms of globus and GORD, and although have been reported cases of malignant transformation this is rare.

Classification

- Prague C&M criteria well validated.
- Locate GOJ by depth of endoscope insertion at level of tops of gastric mucosal folds, and record.
- Look for displacement of squamocolumnar junction above GOJ.
- Measure depth of endoscope insertion at the most proximal circumferential extent of suspected columnar metaplasia.
- Measure depth of endoscopy insertion at maximum extent of suspected columnar metaplasia.
- Subtract depth of insertion for **C**ircumferential and **M**aximum extents from depth of endoscope insertion at GOJ to give **C** & **M** score.

Management

- Aggressive treatment of GORD with → PROTON PUMP INHIBITOR.
- Role of PPIs in patients with asymptomatic Barrett's oesophagus debated, although many believe indirect evidence of benefit strong enough to warrant conventional dose treatment in this group.
- Endoscopic eradication therapy recommended if significant dysplasia present (see also ➔ Barrett's surveillance). These include:
  - *Endoscopic mucosal resection*. For flat and nodular lesions, and early adenocarcinoma limited to mucosa. Can cause strictures, particularly if circumferential segments removed and therefore sometimes used in combination with ablative techniques.
  - *Radiofrequency ablation*. For flat dysplasia or intramucosal carcinoma. Effective and durable, though can cause strictures.
  - *Cryotherapy*. Under evaluation in prospective trials, and occasionally used when radiofrequency ablation has failed.
  - *Photodynamic therapy*. Now rarely used because of complications, and development of less invasive techniques.
- Surgical oesophagectomy largely superseded by endoscopic therapies, unless neoplasia has extended beyond mucosa, or endoscopic therapy failed. May need simultaneous lymph node resection if these are also involved.

Barrett's surveillance

See also: ➢ 'Surveillance' (p. 396).

Most patients with Barrett's oesophagus have normal lifespan and die of unrelated disease. Screening not recommended in general population, but considered in patients with chronic symptoms and multiple risk factors. Endoscopic surveillance recommended to detect ➔ dysplasia and asymptomatic adenocarcinoma, as although cancers in Barrett's oesophagus evolve slowly, endoscopic resection of early disease is extremely effective.

- Quadrantic biopsies every 2cm length of Barrett's oesophagus, and sampling of visible lesions currently recommended. ➢ Chromoendoscopy not proven superior to white light.
- Histopathological dysplasia should be confirmed by two histopathologists. Low-grade dysplasia should be confirmed in two endoscopies. The second endoscopy should be conducted 6mo after first. Addition of p53 immunostain improves diagnostic reliability.

Recommendations

- Barrett's oesophagus shorter than 3cm without intestinal metaplasia or dysplasia should have repeat endoscopy with quadrantic biopsies to confirm diagnosis. If repeat endoscopy confirms absence of intestinal metaplasia, discharge from surveillance encouraged.
- Barrett's oesophagus shorter than 3cm with intestinal metaplasia should receive endoscopic surveillance every 3–5y.
- Patients with segments ≥3cm should have surveillance every 2–3y.
- Those indefinite for dysplasia should be managed with optimized antireflux medication and repeat endoscopy in 6mo. If still indefinite, manage as per non-dysplastic cases.

- Low-grade dysplasia should be re-surveyed at 6mo, and if still present, ablation reduces risk of progression to high-grade disease or adenocarcinoma by 25%.[3]
- High-grade dysplasia and adenocarcinoma confined to the mucosa ideally managed by endoscopic ablative therapies (see ➔ Barrett's oesophagus).
- After ablation for high-grade disease, endoscopic follow-up recommended every 3mo for 1y, then annually thereafter.

Guidelines

BSG guidelines on diagnosis and management of Barrett's oesophagus (2014). 🖱 http://gut.bmj.com/content/63/1/7.long.

BSG recommendation on diagnosis and management of Barrett's oesophagus with low-grade dysplasia (2017). 🖱 http://gut.bmj.com/content/early/2017/04/07/gutjnl-2017-314135.long.

Behçet's disease (see Plate 47)

Named after Hulusi Behçet, Turkish dermatologist (1889–1948). ➔ Vasculitis, affecting several organ systems. Said to occur along old Silk Road from Middle East to Japan. Incidence highest in Turkey (≈400 cases/100,000), Iran (16–100/100,000), and Saudi Arabia and Japan (13/1,000,000). Onset typically in 3rd and 4th decades. More common in ♂ in Middle East but ♀ in Far East. Pathophysiology unknown, though neutrophil function abnormal. HLA-B51 association.

Diagnosis

- Oral aphthous ulcers (recurrent, painful, and non-scarring).
- At least two of:
  - Genital ulcers.
  - Uveitis (anterior or posterior).
  - Skin lesions (pustular vasculitis, ➔ erythema nodosum).
  - Positive pathergy test. Insert sterile 22G needle into skin at three locations on each forearm. Erythematous papules, pustules, or ulcers >2mm after 48h indicate positive result.
- Exclusion of ➔ inflammatory bowel disease, ➔ systemic lupus erythematosus, ➔ reactive arthritis, and herpes.

Clinical features

Oral ulcers almost universal. Other GI involvement reported in 3–16%. Aphthoid ulcers may occur anywhere in tract, but most common in ileocaecal region. Typically <5 lesions. Usually deep and ovoid. Severe complications include perforation and major haemorrhage. ➔ Budd–Chiari syndrome most common hepatic manifestation. Clinical features frequently overlap with ➔ Crohn's disease. Those favouring Behçet's include focal large oval ulcers (rather than segmental disease, cobblestone appearance and diffuse longitudinal lesions); and vasculitis on biopsy rather than granulomas.

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[3] Phoa KN *et al.* (2014). *JAMA* **311**: 1209–17.

Treatment

GI lesions usually treated with → corticosteroids, → 5-ASA, or thalidomide. Doses similar to those used for ➲ Crohn's disease. Limited data on → anti-TNF drugs, but appear effective.[4] Colchicine and azathioprine used for systemic manifestations. Surgery may be required for management of complications.

Beriberi

Clinical manifestation of ➲ vitamin B_1 (thiamine) deficiency. Caused by inadequate intake including: diets high in polished rice (contains thiaminase), ➲ alcohol use disorder (also have ↓ absorption), and rarely (but increasingly) following ➢ antiobesity (bariatric) surgery. Affects cardiovascular system (wet beriberi: oedema, high-output left ventricular failure) and nervous system (dry beriberi: motor and sensory neuropathy, ➲ Wernicke's encephalopathy/Korsakoff psychosis). Historically, thiamine deficiency detected using surrogate marker of ↓ RBC transketolase (requires thiamine as co-factor), but most laboratories can now measure thiamine directly. Treat with IV Pabrinex (2 pairs tds for 5d) followed by oral thiamine supplements (100mg bd).

Bezoars

From Persian word for 'counter-poison', as originally thought to be antidotes for snakebites and insect stings. Defined as persistent concretions of foreign matter in GI tract, nearly always stomach. Can be composed of plant/vegetable fibres (phytobezoars), hair (trichobezoars), or medications (pharmacobezoars: aluminium antacids, enteric-coated tablets, bismuth). Not common, but occur when material enters the stomach but cannot exit because of size, poor solubility, obstruction, or poor motility. Symptoms depend on size and location. May cause bleeding, ulceration, obstruction, and perforation.

Diagnosis

Endoscopy most sensitive test, but may also be detected on AXR, US, or CT. Barium should be avoided as may impede visualization with other techniques.

Management

- Chemical digestion can be tried with cellulase or cola via NG tube.
- Endoscopic disruption can be achieved with forceps and snares, laser, or lithotripters.[5]
- Laparoscopic surgical removal sometimes required.

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[4] Cheon JH & Kim WH (2015). *Curr Opin Rheumatol* **27**: 24–31.

[5] Eng K & Kay M (2012). *Gastroenterol Hepatol (N Y)* **8**: 776–8.

Bile acid malabsorption

Background

- Enterohepatic circulation of bile acids involves excretion from liver into bile of water-soluble conjugated bile acids (cholic and chenoxydeoxycholic acid). Deconjugation by intraluminal gut flora to insoluble dihydroxy bile acids (deoxycholic acid and lithocholic acid) allows 95% reabsorption from terminal ileum and, via portal venous system, circulation back to liver. This conserves bile acids while providing adequate intraluminal concentrations for micelle solubilization and absorption of lipids and fat-soluble vitamins (➲ vitamins A, D, E, K).
- Bile acid malabsorption (BAM) results in excess delivery of bile acids to colon, causing chronic watery diarrhoea.
- Classified into three subgroups:
  - Type 1. Ileal disease: resection, ➲ Crohn's disease, radiation enteritis.
  - Type 2. Idiopathic. May be due to overproduction.
  - Type 3. Secondary to various gastrointestinal diseases, including cholecystectomy chronic pancreatitis, ➲ coeliac disease, ➲ cystic fibrosis, small bowel ➲ bacterial overgrowth, radiation enteropathy.
- Rare primary disease due to congenital deficiency in sodium–bile acid co-transporter.

Clinical features

- Bloating, abdominal discomfort.
- Steatorrhea due to fat malabsorption.
- Diarrhoea. ↑ concentrations of deconjugated bile acids in colon inhibit carbohydrate transporters, reduce intraluminal pH, and directly damage enterocyte.
- ➲ Gallstones. As ↓ bile acid pool and production of lithogenic bile.
- ➲ Oxalate stones.

Investigation

- High level of clinical suspicion often raised by associated clinical problems (e.g. terminal ileal ➲ Crohn's disease). Study of 1,223 patients diagnosed with diarrhoea-predominant ➲ irritable bowel syndrome found 32% to have BAM.
- Most common diagnostic test is selenium homocholic acid taurine (SeHCAT) scan. Se-labelled bile acid administered orally and total body retention measured with γ-camera after 7d. Retention <10% considered abnormal and indicative of BAM.
- There is interest in measuring levels of bile acid precursor, 7α-hydroxy-4-cholesten-3-one (C4). In patients with BAM, bile acid synthesis remains high, reflected by ↑C4. Positive predictive value of serum C4 only 74%, but high negative predictive value (98%) would allow use for excluding BAM.
- In places where diagnostic tests not available, or patients are not keen to undergo investigation, then trial of bile acid sequester and subsequent response can be considered diagnostic.

Management

- Treat underlying cause where possible.
- Bile acid sequesters.
    - → COLESTYRAMINE (starting dose 4g PO od, ↑ by 4g weekly as needed to maximum of 36g/d). Failure to improve diarrhoea within 3d makes BAM unlikely cause of diarrhoea.
    - Two other sequestrants available—colestipol (starting dose 5g PO od) and colesevelam (starting dose 3.75g PO od). Effective, and better tolerated than colestyramine. Standard dose for each can be titrated ↑ or ↓ depending on response.
- Maintain adequate fluid intake to ↓ risk of ➲ oxalate stones.
- Replacement of fat-soluble ➲ vitamins A, D, E, K.

Biliary atresia

Congenital anomaly affecting 1/14,000 live births. Progressive sclerosing, inflammatory cholangiopathy of unknown aetiology.

- Type I. Obstruction of common bile duct.
- Type II. Obstruction of common hepatic duct.
- Type III. Complete obstruction of biliary tree (>90% of cases).

Clinical features

Progressive, conjugated ↑ Bn and hepatomegaly within 1st 3mo of life. Associated with polysplenia, GI, venous, and cardiac malformations.

Diagnosis

Suggested by abdominal US or hepatobiliary scintiscan in neonate with persistent jaundice, and confirmed by cholangiography (via ERCP, transhepatic puncture or, more usually, intraoperatively). Liver biopsy may be characteristic (extrahepatic biliary obstruction).

Treatment

Surgical, usually through ⊳ Roux-en-Y anastomosis (p. 185) with loop of small bowel anastomosed to hepatic ducts at hilum (Kasai portoenterostomy). Effective in >50% but, because of complications (including secondary cirrhosis, progressive ➲ portal hypertension), 10y survival only 35%. ➲ Liver transplantation may be required, either in childhood or early adulthood.

Biliary bypass procedures

See: ⊳'Biliary bypass procedures' (p. 185).

Biliary colic

See ➲ Choledocholithiasis.

Biliary reflux

Reflux into stomach and oesophagus of biliary fluid from duodenum. Alkaline bile irritant to oesophageal squamous mucosa. Factors associated with biliary reflux include duodenal pathology (e.g. distal duodenal stricture), hiatus hernia, and surgery (e.g. Billroth II partial gastrectomy, with bile reflux from afferent loop into stomach). Symptoms similar to those of gastro-oesophageal reflux, but pH oesophageal monitoring (▷ oesophageal manometry) demonstrates ↑ pH in association with symptoms, and acid suppression provides no benefit.

Treatment

- Prokinetic agents: e.g. metoclopramide (see → DOPAMINE RECEPTOR ANTAGONISTS).
- Mucosal protection (→ SUCRALFATE 1g TDS PO).
- Surgery sometimes necessary: ▷ Roux-en-Y anastomosis (p. 185) allows diversion of bile flow further down jejunum.

Biliary strictures

May develop at any point in biliary tree, but site may give clue to aetiology (Table 4.6). For example, low common bile duct (CBD) stricture more likely to be due to ➲ pancreatic cancer or ➲ chronic pancreatitis; mid-CBD to ➲ Mirizzi's syndrome or ➲ gallbladder cancer; and a hilar stricture to ➲ primary sclerosing cholangitis or ➲ cholangiocarcinoma.

Clinical features

Jaundice, RUQ pain, ➲ cholangitis (fever, rigors), abnormal LFTs or, rarely, complications of secondary cirrhosis.

Investigations

- Bloods may show ↑ Bn, cholestatic LFTs (↑ ALP, γGT).
- US accurately demonstrates biliary dilatation, presence of gallbladder stones, and possible mass lesions.
- CT and MRCP are the non-invasive tests of choice to define exact site of stricture, aetiology, and surrounding structures.
- ERCP allows delineation of stricture/biliary tree, cytological brushings, endobiliary biopsies, and therapy (e.g. stone extraction, biliary stenting).
- Cholangioscopy being used more routinely for targeted biopsies and direct visualization.
- EUS, including intraductal miniprobe US, may be available in specialist units, and delineate nature of stricture further (e.g. ➲ cholangiocarcinoma).

Management

Depends on defining cause of stricture (see relevant A–Z sections). Simplistically, involves endoscopic resolution of stricture (e.g. sphincterotomy for ampullary stenosis, balloon dilatation of benign stricture), endoscopic stenting, or surgery (which may include ▷ cholecystectomy for ➲ Mirizzi's syndrome, or biliary bypass procedure).

Bilharzia

See: ➔ Schistosomiasis.

Table 4.6 Causes of biliary strictures

➔ Primary sclerosing cholangitis	➔ Acute/chronic pancreatitis, ➔ Autoimmune pancreatitis/cholangitis (IgG4-related systemic disease)
Malignant: ➔ cholangiocarcinoma, ➔ pancreatic cancer, ➔ gallbladder cancer, ➔ ampullary cancer/stenosis	HIV cholangiopathy (see ➔ HIV and the liver)
Extrinsic compression by hilar nodes	➔ *Clonorchis* infection
Bile duct stone-related stricture/➔ Mirizzi's syndrome	Ischaemic stricture (i.e. secondary to hepatic artery thrombosis post ➔ liver transplantation)
Cholecystectomy-related duct injury	Choledochal varices/cavernoma

Biofeedback

Dyssynergic defaecation is common, affecting up to 50% of people with chronic constipation. Results in inability to coordinate abdominal and pelvic floor muscles to evacuate stool. Biofeedback is a process of behavioural retraining (usually applied in gastroenterology to toileting behaviour) using sensory training, electromyographic, or manometric feedback. Sensory component teaches patient to perceive smaller volumes of rectal distension (often insensible to constipated patients). Motor component performed with pressure probe in anal canal, to monitor sphincter pressure. Patients become accustomed to visual feedback of sphincter activity on voluntary sphincter contraction (can demonstrate failure of sphincter relaxation or failure of pelvic floor function), then many can be taught to improve this). On average 4–6 training sessions required with ≈⅔ of patients, with long-term intractable constipation reporting improvement.[6] Less successful in patients with psychiatric comorbidity or poor compliance with home practice.

Blastocystis

Protozoa, associated with GI symptoms, but clinical relevance speculative as present in many healthy individuals. Pathogenicity may be subtype specific, or may simply be marker of exposure to faecal infection with 'true pathogens' such as *E. histolytica* (see ➔ amoebiasis). 60% of patients with *Blastocystis hominis* but no other stool pathogens have underlying disease associated with some immune compromise (e.g. HIV, organ transplant), and most have symptoms lasting 3–10d. Organism detected on stool microscopy. Reasonable to treat those with persistent diarrhoea where no other pathogens identified. Treatment usually with → METRONIDAZOLE 500mg PO tds for 10d.[7]

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[6] Bassotti G *et al*. (2004). *British Medical Journal* **328**: 393–6.

[7] Roberts T *et al*. (2014). *Gut Pathog* **6**: 17.

Blatchford score

See: ➔ Scoring systems for predicting outcomes in GI bleeds.

Body mass index (BMI)

Defined as body weight (kg) divided by height (m) squared. Correlates well with obesity but not direct measure of adiposity. WHO definitions of body weight categories shown in Table 4.7. See also ► Approach to obesity and ▹ obesity surgery.

Table 4.7 Body weight categories

Category	BMI (kg/m^2)
Underweight	<18.5
Normal weight	18.5–24.9
Mild overweight	25–29.9
Moderate overweight	30–34.5
Severe overweight	>35

Boerhaave syndrome

Named after Herman Boerhaave (1668–1738, Dutch), one of the most revered teachers of his day. Best known for description of oesophageal rupture in Grand Admiral of the Fleet van Wassenaer. Said to have written a book containing all the secrets of medicine. After he died it was opened and all pages were blank except one on which was written: 'Keep the head cool, the feet warm, and the bowels open.'

Clinical features

▲ **Oesophageal rupture** ▲ caused by vomiting against closed glottis. Usually occurs at the weakest point (lower end, left side), but may occur in mid-oesophagus on right. Lack of serosa in oesophagus may make it more prone to rupture. Gastric contents spill into thorax. Pain severe, upper abdominal, and may radiate to back. Examination may reveal dyspnoea, sepsis, hypovolaemic shock, and cyanosis. Surgical emphysema may be found in neck.

Diagnosis

Early diagnosis by clinical suspicion. CXR may show air in mediastinum, and findings confirmed on CT.

Management

- Keep patient strictly NBM and give IV antibiotics (e.g. 3rd generation → CEPHALOSPORIN and → METRONIDAZOLE).
- Early surgery (within 6h) life-saving, Primary closure may be possible if surgery not delayed.

- In late cases, alternatives are drainage with cervical oesophagostomy and gastrostomy, or transhiatal oesophagectomy.
- Endoscopic therapy such as stenting may be considered.
- Mortality for cases diagnosed and treated within 6–12h is 10–15%, rising to >50% for those diagnosed after that time.

Botulism

Pathogenesis

Illness caused by toxins produced by Gram-positive anaerobe *Clostridium botulinum*. Clinical forms include food-borne illness, infant botulism, wound botulism (following trauma or subcutaneous injection of recreational drugs ('skin popping') or, rarely, therapeutic injection of botulinum toxin), and inhalational botulism. Spores common in soil and water, but inactivated by heating to >85°C for >5min. Any that escape this process can then elaborate neurotoxin, which inhibits pre-synaptic acetylcholine release. Canned foods are a particular risk.

Clinical features

Vomiting and diarrhoea within 12–36h, followed by constipation (autonomic paralysis). Bulbar palsy with parasympathetic disruption occurs early, with dry mouth, diplopia, blurred vision, dysarthria, and dysphagia. Weakness then extends to limbs as symmetrical descending paralysis, which includes respiratory muscles.

Diagnosis

- Usually made on clinical grounds.
- Can be confirmed by toxin detection in food, vomitus, or faeces.
- MRI brain/spine, electromyography ± CSF analysis may be required to exclude other diagnoses.

Treatment

Principally supportive, including intubation and mechanical ventilation. Antitoxin available and effective if diagnosed early (Cochrane review 2014. ✎ http://onlinelibrary.wiley.com/wol1/doi/10.1002/14651858.CD008123.pub3/abstract).

Bougies

General term used for dilators of luminal strictures in GI tract. Derived from the Algerian town of Bouginhay, medieval capital of the wax candle trade, because wax dilators were used in the Middle Ages for food impaction. Bougies widely used in ➢ endoscopic dilatation.

Breath tests

See: ➢ 'Breath tests', p. 152.

Budd–Chiari syndrome (BCS)

Definition and pathogenesis

Refers to obstruction of main hepatic veins (HVs) or suprahepatic vena cava. Viewed as separate from ➲ sinusoidal obstruction syndrome, which involves hepatic venules. Diagnosis rarely made unless considered. Causes (Box 4.8) are primary (75%, due to pro-thrombotic disorder) or secondary (related to compression by lesion outside HV).

Clinical features

- Usually presents with abdominal pain, ascites, and hepatomegaly, developing over months. ▲ **Acute liver failure** ▲ may occur.
- Jaundice variable. Features of ➲ portal hypertension, including splenomegaly and bleeding varices, may develop.
- Clinical course varies considerably, but 3y survival of 50% in chronic BCS reported.

Box 4.8 Causes of Budd–Chiari syndrome

- Pro-thrombotic disorders:
  - Antiphospholipid syndrome.
  - Inherited thrombophilias (Factor V Leiden deficiency, protein C/protein S deficiency, antithrombin deficiency, prothrombin mutation G20210A).
  - Paroxysmal nocturnal haemoglobinuria.
- Myeloproliferative disorders:
  - Polycythaemia rubra vera.
  - Essential thrombocythaemia.
- Hyperoestrogenic states:
  - Pregnancy and post-partum state.
  - ➲ Oral contraceptive pill, hormone replacement therapy.
- Chronic inflammatory disorders:
  - ➲ Crohn's disease, ➲ ulcerative colitis.
  - ➲ Vasculitis.
  - ➲ Behçet's disease.
- Tumours:
  - ➲ Hepatocellular carcinoma.
  - ➲ Extrahepatic neoplasms.
- Inferior vena cava webs and stenosis.
- Infections:
  - Aspergillus.
  - Syphilis.
  - Tuberculosis.

Investigation

- Diagnosis usually made with Doppler US or contrast CT (but alert radiologists to clinical possibility).
- Venography and venous pressure measurement allow site of obstruction to be defined. Caudate lobe hypertrophy (due to separate drainage into inferior vena cava) is characteristic, but only seen in 50%.
- Unlike most cases of portal hypertension, ascitic fluid in acute BCS is often an exudate (i.e. SAAG <11g/dl; see ► Approach to ascites).
- Consider thrombophilia screen (see ➲ portal vein thrombosis).

Management

- In acute BCS, thrombolysis and subsequent anticoagulation have been used to attempt to recannulate HVs, but rarely successful.
- In ▲ **acute liver failure** ▲, ➲ liver transplantation may be required.
- Percutaneous transhepatic balloon angioplasty may have role in setting of BCS due to isolated hepatic vein stricture or web.
- In chronic BCS, lifelong anticoagulation required. Management of complications key, including ascites and ➲ portal hypertension. Ascites is diuretic resistant in 30% from presentation. ➲ Liver transplantation probably carries better prognosis than surgical portocaval shunting. ➲ TIPSS has been used to good effect but usually as a bridge to transplantation.

Bulimia

Initially used to describe syndrome of gluttonous overeating and induced vomiting. More recently applied to the psychiatric diagnosis of **bulimia nervosa**, which centres on maladaptive behaviour employed to control calorie consumption and promote weight loss. See also ► Approach to eating disorders. As with ➲ anorexia nervosa, incidence ↑ in recent years. More common than anorexia and estimated to affect 2–5% of school- and college-aged ♀. Depending on behaviour, patients can be categorized into following groups:

- **Purging** Compensation for excessive intake by means of self-induced vomiting and/or ➲ laxative abuse.
- **Non-purging** Binge eating associated with compensatory measures such as excessive exercise, stimulant substances, and/or fasting.

Hallmark personality features are loss of control, low self-esteem, and guilt. Most bulimic individuals are of normal weight and perceive their eating behaviour as problematic, often seeking medical help (unlike patients with ➲ anorexia nervosa). Important physical signs are salivary gland hypertrophy, dental enamel erosion, excoriations on knuckles (Russell sign, caused by digitally-induced vomiting), and chronic sore throat. Medical complications include electrolyte disturbances (hypokalaemia, hypomagnesaemia, hypoglycaemia, hyperprolactinaemia), as well as oesophagitis, pancreatitis, abdominal pain, constipation, and cathartic colon.

B vitamins

See: ➲ vitamins.

Section 4

C

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Campylobacter

Gram-negative spiral bacillus. Among the commonest bacterial causes of gastroenteritis (up to 35%) and accounts for up to 20% of positive cultures in acute dysentery. Two main species responsible: *C. jejuni* and *C. coli*. Principally infect small bowel but can extend to colon.

Epidemiology

Similar to ➔ *Salmonella*. Poultry and eggs are the source in 50–70%. Epidemics may occur if milk or water supplies contaminated. Horizontal transmission frequent. Pathogenesis involves epithelial invasion and toxin production.

Clinical features

Young adults and pre-school children most susceptible. Incubation 1–7d. Prodrome for 24h of fatigue and myalgia; then nausea, marked abdominal cramps and tenderness (may mimic appendicitis), and diarrhoea (can be bloody) is typical. Usually lasts few days but can be protracted. Disease spectrum ranges from asymptomatic carriage to life-threatening colitis with ➔ toxic megacolon. ➔ Reactive arthritis and ➔ haemolytic–uraemic syndrome can occur. ≈30% of patients with Guillain–Barré syndrome have preceding *Campylobacter* infection.

Diagnosis

Stool MC&S.

Therapy

- Fluid and electrolyte replacement (see also: ► Approach to acute diarrhoea).
- Antibiotics:
  - Not beneficial in most cases.
  - Recurrent or severe disease (fever, bloody stools, or severe abdominal pain) can be treated with azithromycin 500mg PO od.
  - → CIPROFLOXACIN 500mg PO bd for 3d is an alternative, although due to overuse in poultry husbandry, resistance reaches 80% in some areas.[1]
  - Early treatment (within 3d of onset) shortens duration by 1.3d.[2]

Candida

Epidemiology

Frequent commensal (found in 40–65% of normal faecal flora). Also most common fungal human pathogen. Clinical syndrome depends largely on host immune status, although there are also fungal virulence factors (Box 4.9).

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[1] Ge B *et al.* (2013). *J Microbiol Methods* **95**: 57–67.

[2] Ternhag A *et al.* (2007). *Clin Infect Dis* **44**: 696–700.

Clinical features

Two main patterns:

- **Mucocutaneous candidiasis** rarely causes death, although patients with refractory HIV infection can become resistant to antifungals, leading to severe oropharyngeal and oesophageal involvement.
- **Disseminated candidiasis** has high mortality but relatively rare.

In GI tract, most common lesions are single or multiple ulcerations, with white plaque and thickened mucosal folds seen at endoscopy. Apart from oropharynx, oesophagus most commonly affected site, but gastric and small intestinal infection can occur. Oropharyngeal candidiasis can be asymptomatic, or present with sore mouth, dysphagia, or retrosternal discomfort. Most common symptom with *Candida* enteritis is diarrhoea. Since organism so often present, small bowel biopsy with histological evidence of invasion necessary for diagnosis.

Differential diagnosis

Includes other diseases affecting GI tract in immunocompromised: other mycoses, ➲ TB, ischaemic bowel, ➲ typhlitis, *Mycobacterium avium*, ➲ cytomegalovirus, ➲ herpes simplex, ➲ lymphoma, ➲ Kaposi's sarcoma.

Treatment

Fluconazole and nystatin commonly used for mucocutaneous disease, including oropharyngeal candidiasis. For disseminated disease, liposomal amphotericin recommended, with fluconazole 2nd line. See → ANTIFUNGALS.

Box 4.9 Risk factors for *Candida*

- Prolonged hospitalization.
- Immunosuppression.
- Parenteral feeding.
- Urinary catheters.
- Broad-spectrum antibiotics.
- → CORTICOSTEROIDS.
- Burns, trauma.
- Recent surgery.
- Haemodialysis.
- HIV (see ➲ HIV and the gut).
- Mechanical ventilation.
- Poorly controlled diabetes.

Carcinoid

Pathology

Well-differentiated neuroendocrine tumours of GI tract (95%), lung, or (rarely) kidneys or ovaries. Account for 1.5% of GI tumours. Secrete range of hormones, including 5-HT (serotonin—metabolized in liver by monoamine oxidase into 5-hydroxyindoleacetic acid (5-HIAA) and excreted in urine), ACTH, histamine, bradykinin, and kallikrein.

Clinical features

Most asymptomatic, but can present with pain, obstruction (20%), ↓ weight (15%), mass (15%), perforation, or haemorrhage (rare).

Carcinoid syndrome arises when hormonal load exceeds capacity of liver to metabolize serotonin. Most have liver metastases or extraintestinal primaries that bypass portohepatic circulation. Clinical features include diarrhoea and abdominal cramps (70%), skin flushing and telangiectasia, or right-sided heart failure from right-sided endocardial fibrosis causing pulmonary valve stenosis and tricuspid regurgitation.

Carcinoids have been classified according to their embryonic origins, as these tumours can behave differently:

- **Foregut carcinoids** Rare. Tumours usually slow growing and benign. Gastric carcinoids classified into:
  - Type I: 70–80%. Small benign tumours associated with chronic ➲ atrophic gastritis, pernicious anaemia, and hypergastrinaemia).
  - Type II: 5%. Large polypoid lesions, prone to metastases, and associated with ➲ multiple endocrine neoplasia type 1 (MEN-1) and Zollinger–Ellison syndrome (see ➲ gastrinoma).
  - Type III. Large solitary sporadic tumours not associated with raised gastrin levels.
- **Midgut carcinoid** Most commonly occurring tumour of small bowel. Ileum most frequently affected site (90%). Tumours may be multiple, and liver metastases occur in 25%. May cause abdominal pain due to intussusception or mesenteric ischaemia.
- **Hindgut carcinoid** Usually non-secretory and not associated with carcinoid syndrome. Colonic carcinoids account for 0.3% of colon tumours; 75% occur in ascending colon. May be incidental finding on examination of removed appendix, usually in patients aged 20–40. In patients with tumour at base of appendix, or if tumour >2cm, right hemicolectomy indicated. In patients with carcinoid at appendix tip, appendicectomy alone is adequate.

Differential diagnoses include ➲ pancreatic endocrine tumours and rare abdominal tumours such as desmoids.

Diagnosis

- 24h urine collection for 5-HIAA is good 1st test (note: may be falsely ↑ by bananas, avocado, pineapple, walnuts, coffee, and chocolate).
- Chromogranin A useful for monitoring progression, response to treatment, and recurrence.; 5-HIAA not accurate for this.
- US not specific, but may lead to more appropriate investigation.
- CT better at providing anatomical information.
- EUS and angiography may be necessary.
- Functional positron emission tomography (PET) scanning increasingly used to identify metastatic lesions.
- OctreoScan or ➢ MIBG (metaiodobenzylguanidine) useful as predictor of clinical response to somatostatin analogues.

Management

Surgical cure may be possible for isolated lesions (or limited liver metastases). For those with carcinoid syndrome, → OCTREOTIDE can effectively control hormone release, but other symptomatic approaches may also be necessary (e.g. loperamide for diarrhoea). Palliative approaches to reduce tumour load include hepatic artery embolization for large hepatic metastases, → INTERFERON ALFA, chemotherapy (e.g. streptozocin, fluorouracil, and doxorubicin), radio-isotope iodine ^{131}I-MIBG, or ^{90}Y-octreotide therapy.

Carcinoid tumours generally slowly progressive. 5y survival >80% in surgically treated patients, and even in those with metastatic disease median survival >2y.

Caroli disease

Congenital multifocal, segmental cystic dilatation of intrahepatic bile ducts, thought to relate to ductal plate malformation and associated with autosomal recessive polycystic kidney disease. Sometimes classified as type 5 ➲ choledochal cyst. Hepatic fibrosis may occur, but extrahepatic tree unaffected. Often presents in early twenties, and clinical features include jaundice, ➲ cholangitis, and intraductal stones. ➲ Cholangiocarcinoma (reported in 7%) and ➲ portal hypertension may develop. Diagnosis often made with non-invasive imaging (e.g. US, CT, MRCP). Endoscopic biliary drainage may be attempted, but of limited use in draining intrahepatic ducts. Hepatectomy effective if disease confined to one lobe, but ➲ liver transplantation may be indicated for recurrent cholangitis and extensive disease.

Caustic ingestion injury

Aetiology and pathogenesis

80% of caustic ingestions occur accidentally in children; ingestion in adults usually indicates intent of suicide or self-harm. Most ingested corrosives are alkaline (bleach and other household cleaning agents) or acids (toilet cleaners, battery acids, swimming pool cleaners). Risks to GI tract are of oesophageal necrosis and perforation, and later sequelae such as oesophageal scarring and stricture formation. However, most deaths following acid ingestion relate to systemic effects (renal failure, liver failure, disseminated intravascular coagulation (DIC)).

- **Acids** cause coagulative necrosis, which lessens tissue penetration. Often cause pylorospasm, so stomach preferentially involved.
- **Alkalis** cause liquefactive necrosis. Immediate severe injuries throughout GI tract.
- Solids adhere to and injure mouth and oropharynx. Liquids rapidly transit through oesophagus to stomach.

Clinical features

Can be dramatic, although severity of symptoms does not correlate well with severity of injury:

- Mouth and chest pain. Absence of pain and oral lesions does not rule out significant GI injury.
- Odynophagia and dysphagia.
- Excess salivation.
- Epigastric pain.
- Concomitant aspiration can cause airway burns.

Management

- Gastric lavage and induced emesis contraindicated as ↑ exposure to corrosive. Similarly supine position should be avoided where possible. Activated charcoal not recommended. Water of no proven use. Do not attempt to neutralize acid or alkali as causes exothermic reaction that exacerbates burn.
- Early assessment of airway and definitive management to secure if compromised.
- Blood tests should include FBC, U&E, LFTs, pH, and lactate. Normal results do not exclude significant transmural necrosis, although deranged results predict poor prognosis. Hydrofluoric acid can additionally cause hypocalcaemia.
- Prophylactic antibiotics often given parenterally, but little evidence.
- No evidence to support routine use of antacid medications.
- CXR may show free air in mediastinum or under diaphragm.
- CT if perforation needs excluding, but if surgical emphysema or peritonism present early surgical exploration is warranted, unless minimal delay in obtaining scan. Currently debated whether CT outperforms endoscopy for selecting patients who require early surgery,[3] but at present OGD remains gold standard.[4]

Endoscopy

- Oropharynx may need to be examined by laryngoscopy, since supraglottic or epiglottic burn with erythema and oedema may be harbinger of airway obstruction and should be seen as indication for early endotracheal intubation or tracheostomy.
- Endoscopy serves dual purpose:
  - Patients with no evidence of GI injury can be discharged, provided that there are no other complications; >50% of patients with history of caustic ingestion have no endoscopic evidence of injury.
  - Those with evidence of severe injury can be actively managed.
- Grading of severity shown in Box 4.10. Predicts systemic complications, mortality, and long-term stricture formation (rare with Grades 0–2a; up to 80% with 3b).

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[3] Chirica M *et al.* (2017). *Lancet* **389**: 2041–52.

[4] Bonnici KS *et al.* (2014). *Clin Toxicol* **52**: 911–25.

- Endoscopy should preferably be performed <12h and generally not >24h after ingestion (although some authors state that endoscopy can be safely performed up to 96h post-ingestion). Severity of mucosal damage on endoscopy within 24h predicts mortality (overall 2–14%, with ↑ rate after acid, due largely to systemic complications—renal/liver failure, haemolysis, DIC). Wound softening begins after 2–3d and lasts up to 2wk, making endoscopy more risky during this period.[5] If required, this should be performed by a senior endoscopist.
- To date, EUS has not improved performance over routine OGD.

Contraindications to endoscopy

- Evidence of full thickness injury, with possible perforation, shock, or acidosis.
- 3rd degree burn of hypopharynx seen at laryngoscopy.
- Perforation complicating endoscopy rare, but attempts to continue past circumferential burns associated with ↑ risk.

Box 4.10 Zargar classification of endoscopic severity of caustic injuries

Grade 0	Normal.
Grade 1	Oedema and hyperaemia of mucosa.
Grade 2a	Superficial localized ulcerations, friability, and blisters.
Grade 2b	Circumferential and deep ulceration.
Grade 3a	Multiple and deep ulceration, small scattered areas of necrosis.
Grade 3b	Extensive necrosis.

Complications of caustic ingestion

- Stricture formation in 15% (correlates with endoscopic staging).
- Fistulation (tracheobronchial and aortoenteric) may occur.
- Early use of IV → CORTICOSTEROIDS may ↓ risk of stricture formation but controversial, and at present not routinely recommended.
- Endoscopic dilatation rarely provides long-term cure, and results with stents unsatisfactory, necessitating surgery in most cases.
- Long-term risk of ➲ oesophageal cancer >1,000-fold higher, developing in up to 30% of patients, with a 40y latency.

Role of surgery

Surgery mandatory if perforation or gastric necrosis, otherwise 50% mortality. Options include oesophagectomy and gastrostomy if stomach intact, or gastrectomy and jejunostomy if stomach is necrotic.

Cestodes

See: ➲ Tapeworms.

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[5] Park KS (2014). *Clin Endosc* **47**: 301–7.

Chagas' disease

See: ➔ Trypanosomiasis.

Child–Pugh score

- Widely used grading system in chronic liver disease, as easy to calculate, uses direct clinical parameters (Table 4.8), and prognostic significance (Table 4.9). Class A regarded as compensated cirrhosis. B as synthetic compromise, and C as decompensated cirrhosis.
- Often used as basis for assessing patients with cirrhosis for ➔ liver transplantation (e.g. Child–Pugh score >7 as indication for referral). Alternative scoring systems that do not rely on subjective parameters (e.g. ascites) increasingly employed (see MELD score in ➔ liver transplantation).

Table 4.8 Child's grading (with Pugh's modifications)

Criteria	Points		
	1	2	3
▲ **Hepatic encephalopathy** ▲ grade	None	1–2	3–4
Serum bilirubin (μmol/L)	<35	35–50	>50
(In ➔ primary biliary cholangitis)	<70	70–170	>170
Serum albumin (g/L)	>35	35–28	<28
Prothrombin time prolongation (sec)	1–4	4–10	>10
or			
INR	<1.7	1.7–2.3	>2.3
Total score	**5–6**	**7–9**	**10–15**
Child's grade equivalent	**A**	**B**	**C**

Table 4.9 Percentage survival in chronic liver disease

Child's grade	1 year	5 years	10 years
A	84	44	27
B	62	20	10
C	42	21	0

Cholangiocarcinoma

Definition and pathogenesis

- Malignancy arising from biliary tree; 1.5% of all cancers. Rate increasing. Important cause of ➲ biliary strictures.
- Associations include ➲ primary sclerosing cholangitis (PSC) (>20% of patients with long-standing PSC develop cholangiocarcinoma, but PSC associated with only 5% of cases), ➲ gallstones, ➲ choledochal cysts, ➲ Caroli's disease, and biliary infestation with oriental liver flukes ➲ *Clonorchis sinensis* or *Opistorchis viverrini*. Chronic ➲ hepatitis B and ➲ hepatitis C ↑ risk 2–4-fold.
- Approximately 20–25% of tumours intrahepatic, 50–60% perihilar ('Klatskin' tumours involve confluence of left and right hepatic ducts in 20%), and 20–25% distal bile duct.
- See Fig. 4.5 for Bismuth classification.

Clinical features

Abdominal discomfort, weight loss, and obstructive jaundice are the most common presenting symptoms, similar to ➲ pancreatic cancer.

Investigations

- See ► Approach to recent-onset jaundice.
- Site, size, and vascular involvement of tumour may be demonstrated with CT and MRCP. Biliary anatomy well shown with MRCP, but ERCP allows tissue sampling and endoscopic stenting.
- Tissue diagnosis can be made at ERCP by endoscopic biopsies or brushings, or EUS-directed fine needle aspiration/biopsy. Percutaneous biopsy usually reserved for cases where surgical cure is not feasible. Biliary cytology has sensitivity <40%. Directly visualized targeted intrabiliary biopsies possible with cholangioscopy.
- Tumour marker ▷ CA19-9 ↑ in 85% of cases, but diagnostic role limited as may be elevated in biliary obstruction of any aetiology. Staging by ➲ TNM classification.

Management

- Surgical resection with cure possible in only 10–15% of cases. 5y survival post-surgery 9–18% for proximal tumours, 20–30% for distal bile duct lesions. ➲ Liver transplantation rarely performed (because of very high rates of recurrence), but very highly selected patient groups may have up to 82% 5y survival, with emerging data on aggressive neoadjuvant therapy prior to transplantation showing some promise. Patients should be given option of enrolling in a clinical trial if they fulfil entry criteria.

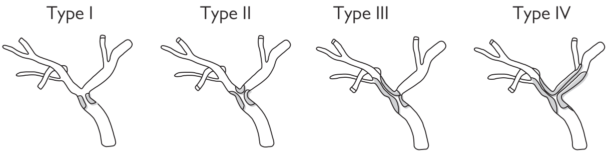

Fig. 4.5 Bismuth classification of cholangiocarcinoma. Type I, involvement of common hepatic duct, but below confluence of right and left ducts; type II, involvement of origin of left and right ducts at confluence; type III, involvement of secondary left or right intrahepatic ducts; type IV, involvement of secondary intrahepatic ducts bilaterally.

- Effective palliative endoscopic or percutaneous transhepatic stenting (plastic or self-expanding metal stents) vital to preserve liver function and prevent cholangitis.[6] Palliative resection carries significant morbidity; not superior to endoscopic or percutaneous biliary drainage, and should therefore only be considered in patients with high performance status in whom such procedures have failed.
- For palliative therapy, gemcitabine + cisplatin used for patients not suitable for clinical trials (which are ongoing as currently no convincing evidence for use of any one regimen).
- Maintaining biliary drainage is a crucial determinant of survival, with use of percutaneous or endoscopic biliary stenting ± biliary radiofrequency ablation (RFA) to maintain stent patency.

Cholangitis

Infection of biliary tree, usually arising from combination of biliary obstruction (e.g. ➔ biliary stricture) and presence of bacteria (usually Gram-negative gut flora).

Aetiology and pathogenesis

Causes of obstruction include stones (see ➔ choledocholithiasis), biliary strictures (e.g. ➔ primary sclerosing cholangitis, ➔ pancreatic cancer, ➔ cholangiocarcinoma), infestation (e.g. ➔ *Clonorchis*), and following instrumentation (particularly if incomplete drainage at ERCP).

Clinical features

Classic Charcot triad includes fever (>90% of cases), jaundice (65%), and RUQ pain (>40%). Presence of all three strongly favours diagnosis, but combination occurs in <20% of cases at presentation. Septic shock and confusion may occur. Secondary complications include acute renal failure, DIC, and ➔ liver abscess formation.

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[6] Witzigmann H *et al.* (2008). *HPB (Oxford)* **10**: 154–60.

Investigation

- FBC shows ↑ WCC (↑ neutrophils).
- U&Es: renal failure associated with septic shock.
- LFTs: ↑ bilirubin and predominantly cholestatic pattern (↑↑ ALP/γGT), but ↑ ALT/AST often present.
- Blood cultures positive in up to 50%.
- Urgent US or CT scan showing biliary dilatation in correct clinical setting strongly supports diagnosis. Loss of aerobilia (air in biliary tree) in patient with biliary stent *in situ* suggests blocked stent.
- After demonstration of dilated bile ducts, ERCP allows confirmation of biliary obstruction and therapy.

Management

- Fluid resuscitation and management in high dependency area if hypotensive with signs of septic shock.
- Broad-spectrum IV antibiotics (e.g. IV → CEPHALOSPORIN + → METRONIDAZOLE or → PIPERACILLIN/TAZOBACTAM), but note antibiotics alone rarely resolve cholangitis in presence of ongoing biliary obstruction.
- ERCP with biliary decompression (e.g. biliary sphincterotomy and stone removal/stent insertion) essential. Percutaneous transhepatic drainage (PTD) only used if ERCP fails or technically impossible, as complications higher (and puncture often ↑ bacteraemia acutely).
- Mortality rates of 7–40% reported, which relate largely to delayed intervention and complex biliary stricturing (e.g. complex hilar stricturing due to hilar ➲ cholangiocarcinoma).

Cholecystitis

Inflammation of the gallbladder, which results from obstruction of the cystic duct by ➲ gallstones in 90% of cases. Cystic duct obstruction may occur secondary to ➲ cholangiocarcinoma or other causes of ➲ biliary stricture, and occasionally following insertion of mesh metal biliary stent. Acalculous cholecystitis is related to biliary stasis (e.g. following major surgery/trauma, sepsis, ➲ parenteral nutrition, ➲ sickle cell anaemia, diabetes mellitus, ➲ HIV). Bacterial infection thought to be secondary to obstruction.

Clinical features

Most patients have prior history of biliary colic (see ➲ gallstones), but pain of acute cholecystitis more constant and severe, and lasts for >6h. Settles in most cases after 1–4d.

- Fever, nausea, and vomiting often present.
- Examination may reveal fever and tachycardia, with tenderness in RUQ, with guarding and rebound. Palpable gallbladder in 30%.

- To elicit Murphy's sign, place examining hand underneath right costal margin in mid-clavicular line and ask patient to breathe in; patient will discontinue inspiration on contact of hand with an inflamed gallbladder. To confirm finding, pain should not be elicited on performing manoeuvre on left side. The findings can be reproduced at the time of ultrasonography.
- Jaundice suggests ➲ choledocholithiasis or ➲ Mirizzi's syndrome.
- Gallbladder perforation occurs in 10–15% of cases, and ➲ gallbladder empyema may occur.

Investigation

- ↑ WCC (neutrophilia) common.
- ↑ ALP in 25%, but deranged LFTs usually suggest associated biliary obstruction (common bile duct (CBD) stones in 10% of patients with calculous cholecystitis).
- Transabdominal US >90–95% sensitive, 80% specific. Diagnosis suggested by pericholecystic fluid, gallbladder wall thickening >4 mm, and presence of gallstones. Wall thickness unreliable in patients with ascites and hypoalbuminaemia.
- CT 95% sensitive and specific. Although less effective than US in detecting gallstones, more accurate in identifying complications (e.g. gallbladder perforation, empyema).

Management

- In acute phase, admit and keep NBM with IV fluids.
- Antibiotics: a 3rd-generation intravenous cephalosporin + metronidazole if septic; otherwise co-amoxiclav or ciprofloxacin appropriate.
- Cholecystectomy (see ⊳ 'Cholecystectomy', p. 184). Outcomes usually best if delayed until acute inflammation settled; most patients should be referred for laparoscopic cholecystectomy 6–8wk after resolution of cholecystitis, but immediate surgery mandated in patients with frequently recurrent disease, or ➲ acute pancreatitis due to gallstones.

Choledochal cyst

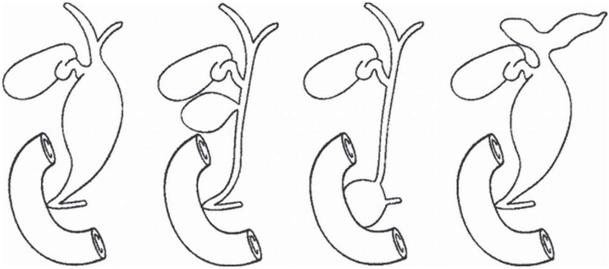
Cystic dilatation of intra/extrahepatic bile ducts. Particularly reported in Far East. Classified into several types (Fig. 4.6).

Clinical features

Majority of patients present at <30y, with pain and jaundice, or as incidental finding on imaging. Complications include rupture, ➲ cholangitis, cirrhosis, ➲ acute pancreatitis, ➲ portal hypertension, and ➲ cholangiocarcinoma (up to 50% of untreated patients by age 50).

Investigation

Diagnosis usually made by CT, MRCP, or ERCP.



Type 1 Type 2 Type 3 Type 4

Fig. 4.6 Choledochal cysts. Type 1, diffuse or fusiform dilatation of extrahepatic bile ducts (93% cases); Type 2, diverticulum arising from bile duct; Type 3, cystic dilatation of distal bile duct, within duodenum; Type 4, type 1 + intrahepatic cyst; Type 5, ➲ Caroli's disease.

Management

Complete cyst excision essential (in part to ↓ risk of cholangiocarcinoma), with ➢ Roux-en-Y hepaticojejunostomy (p. 185). Recurrent symptoms common, and secondary biliary cirrhosis may require ➲ liver transplantation.

Choledocholithiasis (see Plate 39)

Aetiology and pathogenesis

In 85% of cases, CBD stones have formed in gallbladder and then passed into CBD via cystic duct (secondary stones). Primary stones within bile duct may occur in association with biliary inflammation and/or bile stasis (e.g. ➲ primary sclerosing cholangitis, ➲ choledochal cyst, ➲ biliary strictures, ➲ *Clonorchis* infection).

Clinical features

- Asymptomatic stones found in 7% of patients undergoing cholecystectomy, but symptoms develop in up to 50% if left in CBD.
- Obstructive jaundice, often associated with colicky RUQ pain, common. Pain, nausea, and vomiting often precede jaundice, which is associated with dark urine and pale stools. Examination reveals jaundice and RUQ tenderness. Palpable gallbladder unusual, and suggests cause of CBD obstruction other than stones (see 'Courvoisier's law' in ➲ pancreatic cancer).
- ➲ Acute pancreatitis (AP): passage of stones cause 50% of cases of AP, and complication occurs in 4–8% of patients with gallstones.
- ➲ Cholangitis: suggested by jaundice and fever. Unusual in patients with choledocholithiasis *per se*, but more common in association with biliary intervention (e.g. post-ERCP).

Investigation

- See also ➲ acute pancreatitis, ➲ cholangitis, ▶ Approach to recent-onset jaundice.
- In patients with obstructive jaundice, LFTs show ↑ bilirubin, and predominantly cholestatic derangement (↑↑ ALP, γGT) (although ↑ ALT/AST often also present).
- Abdominal US 1st line test, but only 50% sensitive in detecting CBD stones; much more accurate at detecting CBD dilatation. MRCP risk-free (in contrast with ERCP), with 60–90% sensitivity for bile duct stones. May fail to detect stones <5mm, but ↑ role in patients with low to intermediate chance of CBD stones.
- ERCP >95% sensitive and specific for CBD stones. Only indicated in patients with high probability of bile duct stones (e.g. dilated CBD on US, jaundice, gallbladder stones) as allows therapeutic intervention.
- EUS very useful for low to intermediate chance of CBD stones, with sensitivity/specificity comparable to ERCP, but without the risk.
- CT has sensitivity of 75–90% in detection of CBD stones.

Management

ERCP allows performance of biliary sphincterotomy and stone clearance in 85–90% of cases. Reasons for failure to clear stones include altered duodenal anatomy (e.g. Billroth II Polya gastrectomy: see ➢ 'Gastrectomy', p. 183), or large (>1.5cm) impacted bile duct stones. Bile duct stenting performed if stone cannot be removed at ERCP.

- Cholecystectomy should be considered in all patients with secondary CBD stones, usually after ERCP and stone clearance. In expert hands laparoscopic cholecystectomy and bile duct stone clearance have high rate of success. Avoids added risks of further ERCP.
- In patients unfit for surgery, ERCP and biliary sphincterotomy can be performed without cholecystectomy, but >30% develop further episodes related to stones over 5y period.
- Cholangioscopy and direct electrohydraulic lithotripsy may allow dissolution of impacted stones (see ➢ 'Cholangioscopy', p. 212).

Cholera

Acute secretory diarrhoea caused by *Vibrio cholerae* O1 or O139. Endemic in >50 countries; also causes large epidemics. Recent wave attributable to atypical El Tor strains. Kills 100,000/y in Asia, Africa, and Latin America. Children aged 2–9 and women of childbearing age at highest risk. Contaminated water is the main route of transmission; person-to-person rare. Blood group O increases susceptibility.

Diagnosis

Usually presumptive**,** or by laboratory identification (stool culture or serology) of toxigenic vibrios.

Clinical features

Ingested cholera colonizes the small intestine**. P**roduces exotoxin that activates adenylate cyclase, ↑ cAMP, and stimulates chloride secretion and ↓ sodium reabsorption. Most infections asymptomatic or mild, but can produce large-volume (up to 1L/h) watery diarrhoea ('rice water' stool). Vomiting common; fever and abdominal pain unusual (suspect secondary infection). Complications: dehydration, metabolic acidosis (bicarbonate loss in stool, lactic acidosis from hypoperfusion; manifests with Kussmaul breathing), hyponatraemia, hypokalaemia, hypocalcaemia, hypoglycaemia, and fits. 'Cholera sicca' is an atypical form of disease in which fluid accumulation in intestinal lumen leads to circulatory collapse prior to passage of 1st loose stool.

Therapy

WHO ➲ oral rehydration solution is effective in 95%, although patients need rapid access (in Haiti epidemic of 2010, median time from symptom onset to death was 12h). Those with severe dehydration or fluid losses >10ml/kg/h should initially have IV fluid and electrolyte replacement, aiming to replace baseline fluid deficit within 3–4h. Oral rehydration should begin as soon as possible afterwards, as more potassium, bicarbonate, and glucose available in these solutions than in standard IV fluids. Administer 0.25–0.5g/kg IV glucose if symptomatic hypoglycaemia.

Antibiotics ↓ volume and duration of diarrhoea by 50%. Although historically not advocated, now recommended if moderate or severe dehydration, or to limit infectivity during epidemics. Choice depends on local resistance patterns. May include tetracycline 500mg qds for 3d (resistance common, avoid in pregnancy or children), ciprofloxacin 500mg bd for 3d, or azithromycin 1g single dose. Zinc supplementation has similar impact in children; WHO recommend 10mg/d for infants <6 months and 20mg/d if 6 months-5y.[7]

Outcome

Mortality >50% untreated, but <0.2% with appropriate therapy. Higher case fatality in immunologically naïve populations. Hypoglycaemia and ↓ GCS are risk factors for death. Full recovery without antibiotics in most in 1–6d with adequate rehydration. Symptomatic patients shed organisms in stool for 2–14d.

Vaccination

Three oral vaccines available, which have superseded injectable vaccines. Ultimately key to disease eradication is safe access to water and sanitation.

Chronic granulomatous disease (CGD)

Rare genetic immunodeficiency (1/250,000), in which phagocytes are unable to kill bacteria and fungi due to defects in electron transport chain underlying respiratory burst. Classified by mode of inheritance and component of NADPH oxidase affected: 65% X-linked, remainder autosomal recessive. Majority of patients ♂.

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[7] Harris JB *et al.* (2012). *Lancet* **379**: 2466–76.

Clinical features

Usually presents with recurrent severe infections from infancy, although phenotype can be mild with diagnosis delayed until adulthood. GI involvement in 50–80% of patients with granuloma formation due to inadequate clearance of microbial antigens. Ulceration may arise anywhere in GI tract, but has predilection for distal colon and rectum, often in patchy distribution. High frequency of pyloric obstruction and perianal disease. In many cases, phenotype clinically, radiologically, and pathologically indistinguishable from ➲ Crohn's disease.[8] This offers a tantalizing clue to possible pathogenic mechanisms in ➲ Crohn's disease, with growing body of genetic, laboratory, and clinical data suggesting that failure to adequately clear bacteria from mucosal tissues could be common to both.

Diagnosis

Screen with nitroblue tetrazolium (NBT) test. Can get false positives and negatives, therefore confirm with quantitative biochemical assay for respiratory burst (cytochrome c reduction or oxygen electrode), and molecular assay for absent gene/protein.

Management

Treatment of GI disease not well defined, but generally follows that for idiopathic ➲ Crohn's disease, with → CORTICOSTEROIDS 1st line and steroid-sparing immunomodulators such as → AZATHIOPRINE for long-term maintenance. Infliximab has been successfully used for recalcitrant disease, but can predispose to severe (and in some cases life-threatening) infection, mandating aggressive antimicrobial prophylaxis and assiduous vigilance.[9] Treatment with interferon-gamma ↓ infections but not GI inflammation. In refractory cases, haematopoietic stem cell transplantation can be considered. Gene therapy has reached Phase 1/2 clinical trials and demonstrated therapeutic potential, but stalled due to lack of sustained benefit and high rates of insertional mutagenesis causing secondary myeloid malignancy.

Long-term prognosis has improved markedly with use of prophylactic antibiotics and antifungals. While historically many died in childhood, survival to age 20y now ~90%. This falls to 50% by the end of middle age, but thereafter there is a survival plateau.

Chronic pancreatitis

Definition and aetiology

Benign disease characterized by permanent alteration of anatomy and function of pancreas due to chronic inflammation. Causes include ➲ alcohol (>70%), tropical pancreatitis (onset <40y in equatorial regions; may be linked to protein energy malnutrition), pancreatic duct obstruction (e.g. tumours, intraductal stones, traumatic strictures), ➲ hereditary pancreatitis, idiopathic chronic pancreatitis (20%), intraductal papillary mucinous tumour (IPMT—see ➲ pancreatic cystic tumours), ➲ cystic fibrosis, and ➲ autoimmune pancreatitis. Episodes of ➲ acute pancreatitis may occur during course of chronic disease.

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[8] Marks DJB *et al.* (2009). *Am J Gastroenterol* **104**: 117–24.

[9] Uzel G *et al.* (2010). *Clin Infect Dis* **51**: 1429–34.

Clinical features

- Epigastric pain, often radiating to back, associated with anorexia and weight loss. Pain resolves in 80% within 10y of onset, often in parallel with development of endocrine and exocrine ➔ pancreatic insufficiency.
- Insulin-dependent diabetes develops in 40–70% of patients.
- Steatorrhoea (pale loose foul-smelling stools, difficult to flush).

Investigation

Diagnosis made by assessing pancreatic structure and function. Serum amylase typically normal/only minimally raised.

Structure

- AXR may show pancreatic calcification (25–60% of cases).
- CT, MRCP, ERCP, and EUS are complementary, and may show anatomical features of chronic pancreatitis: irregular main pancreatic duct with dilatation and/or strictures; side-branch irregularity; pancreatic parenchymal heterogeneity, enlargement, or atrophy.

Function

- Functional abnormalities in chronic pancreatitis include ↓ in stimulated secretory capacity, exocrine insufficiency (maldigestion and steatorrhoea), and endocrine insufficiency (diabetes mellitus).
- MRCP with secretin: ↓ secretin output or obstruction of flow due to pancreatic stricture may be seen.
- Fasting glucose/glucose tolerance test.
- Serum ➔ vitamins A, D, E, K.
- Faecal elastase-1 produced by pancreas and passed in stool largely unaltered (and unaffected by coadministration of → PANCREATIC ENZYME SUPPLEMENTS). Highly sensitive and specific for exocrine function (except for falsely low levels with significant diarrhoea) and much easier to perform than urine pancreolauryl test or 3-day faecal fat (also see ➔ pancreatic insufficiency).

Management

- Remove precipitant (where applicable, e.g. alcohol).
- Pain control. Start with non-opiates (e.g. paracetamol, NSAIDs), cautiously increasing to mild → OPIATES (e.g. codeine, tramadol) then stronger opiates (e.g. morphine, immediate and slow release). Endoscopic removal of stones from pancreatic duct in head of pancreas may occasionally help. Coeliac plexus block (percutaneously or via EUS) may be effective. In setting of pain and dilated pancreatic duct, surgery (e.g. drainage procedure—Frey's, Peustow) provides better long-term palliation than endoscopy.[10]
- Treat diabetes (most patients require insulin, although doses may be low, due to associated loss of glucagon-producing α cells).
- In patients with exocrine insufficiency, oral → PANCREATIC SUPPLEMENTS with meals (e.g. Creon®, Nutrizym®) help ↓ weight loss, malabsorption, and steatorrhoea. Give with → PROTON PUMP INHIBITOR to ↓ inactivation of enzymes in stomach.

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[10] Cahen DL *et al.* (2007). *New Engl J Med* **356**: 676–84.

- Endoscopic stenting of ➲ biliary strictures may be required, but if no improvement in 12–18mo, consider surgery (see ⊳ 'Biliary bypass procedures', p. 185).
- Nutritional support (including fat-soluble vitamins).
- Surgery, including pancreatic resection (e.g. Whipple's procedure) or drainage procedure, occasionally indicated for pain or complications (e.g. duodenal obstruction, ➲ pancreatic pseudocyst formation).

Complications

- ➲ Portal vein thrombosis and ➲ portal hypertension in 1%.
- Jaundice due to low ➲ biliary stricture.
- ➲ Pancreatic pseudocyst formation.
- ➲ Pancreatic cancer develops in ≈3% (8-fold ↑ risk).
- Life expectancy shortened by 10–20y.

Cirrhosis

See: ► Approach to cirrhosis and chronic liver disease.

Clonorchis infection

Chinese liver fluke (*Clonorchis sinensis*). Infects 30 million people worldwide, mainly in SE Asia. Life cycle involves passage of eggs in human faeces, ingestion by snails, subsequent ingestion of cercariae by fish, and consumption of fish and encysted larvae by humans. Adult worms 10–25mm long induce inflammatory response in biliary tree where they may persist for 30y, leading to ➲ biliary strictures and obstruction, recurrent ➲ cholangitis, ➲ choledocholithiasis, secondary biliary cirrhosis, and ➲ cholangiocarcinoma. Diagnosis suspected in patient from high-risk area with unexplained biliary stricturing/cholangitis, and confirmed on isolation of eggs in stool or duodenal aspirate. Treatment with praziquantel or albendazole, but biliary lesions may persist.

Clostridial infections of the GI tract

Gram-positive anaerobic rods. Spores can survive many extreme environmental conditions, prior to acquisition in humans by ingestion. For *C. botulinum* see ➲ botulism.

C. difficile-associated diarrhoea (CDAD)

- *C. difficile* discovered in 1935 but only linked with antibiotic-associated diarrhoea in 1978. Found in stools of healthy newborns, but seldom part of normal adult commensal flora. Colonization often follows antibiotic ingestion, cancer chemotherapy, or infection by other pathogens (➲ *Salmonella*, ➲ *Shigella*).
- In recent years hypervirulent, drug-resistant strain (NAP1/BI/027) associated with large outbreaks of severe disease, with higher mortality (10%). Produces 20-fold more toxin, and can cause disease in those without risk factors, including healthy young adults.

- GI damage caused by two exotoxins, A and B. They are cytotoxic, destroying actin filaments.
- Rates of carriage ↑ since 2000. Asymptomatic carriage now detected in 5% of healthy adults, 7% of hospital patients on admission (rising during stay, although only 30% of these develop diarrhoea), and up to 57% of care home residents.

Risk factors

- Antibiotics. First seen with clindamycin, but co-amoxiclav, cephalosporins, and ciprofloxacin now most frequently implicated. Any antimicrobial that disrupts intestinal microflora can trigger CDAD.
- Drugs that inhibit gastric acid secretion (PPIs, H_2RAs).
- Extremes of age. recent GI surgery, malignancy, IBD, immunocompromise and prolonged hospital stay.

Clinical features

- Spectrum of disease ranges from:
  - *Diarrhoea*. Watery but not bloody. Sometimes accompanied by lower abdominal cramps. Endoscopy usually normal.
  - *Colitis*. Most common clinical manifestation. Patients usually have fever, malaise, abdominal pain, and high-volume watery diarrhoea, sometimes with trace of blood. Leukocytosis common. Sigmoidoscopy shows patchy colitis without pseudomembranes.
  - *Pseudomembranous colitis*. Systemic illness with severe bloody diarrhoea, abdominal pain and tenderness, and fever. Hypoalbuminaemia can result from acute phase response and protein loss.
  - *Fulminant colitis*. Up to 3% of patients. Presents with paralytic ileus and toxic megacolon. Can progress to perforation.
- Diarrhoea and abdominal cramps usually occur within 1st week, but can be delayed up to 6 weeks.
- Fulminant colitis can present acutely in previously well, or during course of milder infection. Look for fever, tachycardia, tenderness, guarding, and reduced bowel sounds. Plain radiograph may show ➔ toxic megacolon, and bowel wall may be thickened on CT.
- *C. difficile* infection can complicate ➔ Crohn's disease and ➔ ulcerative colitis: 5–25% incidence of toxin-positive stools reported, not always after antibiotic exposure. Always get stool for *C. difficile* toxin in patients with relapses of IBD. Increases rates of emergency colectomy and mortality.
- Case fatality 2.3%. Recurrent infection increasingly pervasive with 33% readmission at 90d.[11]

Diagnosis

- Only stools from patients with diarrhoea should be tested.
- PCR based testing for organism should be standard diagnostic test, followed by immunoassays for toxins A and B. Stool culture takes 2–5d, but generally not required.
- Patients who are *C. difficile* PCR antigen-positive but toxin-negative may either have asymptomatic carriage or early infection. Only treat if diarrhoea present; otherwise manage expectantly.

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[11] McDonald LC *et al.* (2006). *Emerg Infect Dis* **12**: 409–15.

- Flexible sigmoidoscopy and biopsy may demonstrate pseudomembranes and typical histological appearances; simple proctoscopy is insufficient as rectum spared in 30%. Characteristic finding of yellow–white raised plaques, 2–5mm in diameter, in pseudomembranous colitis (Plate 25), although these often occur proximal to sigmoid colon. Biopsy shows 'summit lesions': outpourings of pus from micro-ulceration of surface epithelium.
- If pre-test suspicion of CDAD sufficiently high, initiate treatment empirically as negative predictive values of assays insufficient to exclude disease in these patients.
- Serial testing, or testing for proof of cure, not recommended unless diagnostic uncertainty in patients who were antigen-positive, toxin-negative with ongoing diarrhoea.

Management

- Infection control paramount. Isolate patients in side-room with barrier precautions. Avoid fomite spore transfer (keep medical notes and charts outside).
- Stop any inciting antimicrobial agent, if possible. In patients with IBD on immunosuppression, the latter can be maintained while antibiotic treatment is initiated but should not be escalated.
- Avoid antiperistaltic agents (e.g. loperamide) as precipitate complications of disease.
- Request AXR and VBG if ≥2 severity markers present (see Box 4.11). Serial imaging, CT, and surgical review necessary in fulminant colitis; suspect if several severity markers present ± lactate raised.
- Monitor FBC, U&E, and Mg regularly.
- Oral → METRONIDAZOLE 400mg PO tds for 10–14d 1st line in patients without severity markers. Can use 500mg IV tds in patients who are NBM, have ➲ ileus or severe malabsorption, but otherwise this is less effective than oral therapy. Failure to respond within 5–7d should prompt a change in agent to Vancomycin.
- Vancomycin 125mg PO qds in severe or relapsed disease. Short-term cure rates ≈95%. Increase to 500mg PO/NG qds + metronidazole 500mg IV tds if hypotension, shock, or megacolon, and obtain surgical consult. Vancomycin enemas (500mg in a volume of 500ml qds) can be used if delivery to large bowel disrupted (e.g. in presence of ileus or ileostomy).
- Escalate therapy in patients with multiple relapses. Involve microbiologist in these decisions, as little data to guide choice of therapy. Duration guided by symptoms. Options include:
  - Vancomycin 500mg PO qds, tapering over 6 wk.
  - Vancomycin 125mg PO qds + metronidazole 400mg PO tds.
  - Fidaxomicin 200mg PO bd for 10d.
- Toxin-binding polymers (e.g. tolevamer) less effective than antibiotics. Monoclonal antibodies against *C. difficile* may ↓ recurrence.[12]
- Colectomy may be necessary in fulminant colitis.

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[12] Wilcox MH *et al.* (2017). *New Engl J Med* **376**: 305–17.

- Relapse occurs in 20% of successfully treated patients. Consider withholding further antibiotics to allow normal flora to re-establish. Moderate quality evidence supports use of probiotics in relapse prevention. No specific preparation proven to be more effective (see Cochrane review 🖱 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006095.pub4/full).
- Faecal microbiota transplant looks promising in patients who have multiple recurrences,[13] although quality of evidence to date limited.
- No proven benefit in treating asymptomatic carriers.

Box 4.11 Markers of severity of CDAD

- Age >60.
- WCC $>15\times10^9$/L.
- Temperature >38.5°C.
- Albumin <25g/L.
- Hypotension or tachycardia.
- Oliguria or eGFR <40mL/min.
- Ileus (may mask fluid losses)*.
- Stools >10/d*.
- Colonic dilatation on AXR*.
- Abdominal distension or tenderness.

*Markers suggestive of fulminant colitis

Guideline

American College of Gastroenterology guideline on diagnosis, treatment, and prevention of *C. difficile* infection (2013). 🖱 https://www.nature.com/articles/ajg20134.

Clostridium perfringens

- Food-borne pathogen, causing gastroenteritis through enterotoxin produced by *C. perfringens* type A. 90% of cases caused by meat or poultry cooked adequately but then left to stand for 4–24h and served cold or poorly rewarmed. Abdominal cramps and diarrhoea occur within 8–12h of ingestion, followed by recovery within 24h.
- Implicated in some cases of antibiotic-associated diarrhoea, and putative but unproven association with necrotizing enterocolitis in neonates.
- Sporadic outbreaks, especially in Papua New Guinea where disease is called pigbel, result from feasting on poorly cooked pork contaminated with *C. perfringens* type C. Vaccine preventable. Treat with high-dose benzylpenicillin and metronidazole.

Coccidia

Intracellular protozoa. Genera *Cryptosporidium, Cyclospora* and *Cystoisospora* cause acute self-limiting diarrhoeal illness in immunocompetent hosts, and severe chronic diarrhoea in immunocompromised. All replicate within enterocyte and biliary epithelium, and shed cysts or spores into stool.

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[13] Kassam Z *et al.* (2013). *Am J Gastroenterol* **108**: 500–8.

Cryptosporidium

Identified as a human pathogen in 1976. During 1980s, recognized as major cause of chronic diarrhoea in AIDS patients; zoonotic and large waterborne outbreaks; and acute diarrhoea in children. By 1990s, known to be ubiquitous (global distribution, oocysts resistant to water chlorination and most disinfectants).

Eight species infect humans; *C. hominis* and *C. parvum* responsible for most cases. Children <2y most frequently and severely affected (accounts for 9% of diarrhoeal illness; malnutrition is both consequence and risk factor). Common in HIV (risk evident when CD4 <200/mm^3, though much more marked when <100/mm^3), congenital T-cell immunodeficiency and transplant patients (can be difficult to distinguish from ➔ GvHD).

Clinical features

Mean incubation: 5–7d; disease duration: 9–22d.[14] Causes high-volume watery diarrhoea ± mucus and abdominal cramps. Extraintestinal manifestations rare in immunocompetent, but ➔ cholecystitis in 10% of AIDS patients and implicated in HIV cholangiopathy (see ➔ HIV and the liver).

Diagnosis

Stool microscopy for oocytes (send 3 samples on alternate days). Sensitivity enhanced by modified acid-fast or fluorescent staining; often not routinely performed therefore alert laboratory to possible diagnosis. Stool antigen and PCR tests available.

Therapy

Fluid replacement. Limited role for antibiotics: infection self-limiting in immunocompetent and often resolves following introduction of HAART for HIV (protease inhibitors may also specifically impede parasite development and invasion). Some evidence for nitazoxanide 500mg bd for 14d (patients without HIV) and paromomycin 500mg qds for 14d (HIV-infected patients) in recalcitrant cases. Highly infectious, so advise strict hand hygiene, exclusion from school or workplace until >48h after last diarrhoeal episode, and avoid swimming until 2wk after resolution.

Cyclospora cayetanensis

Discovered in 1980s. Common cause of diarrhoea in AIDS in developing countries (prevalence 0.2–4.3%), but rare in developed countries. Sporadic outbreaks reported, peaking in summer months.[15]

Clinical features

Comparable to cryptosporidiosis.

Diagnosis

Stool microscopy: 8–10μm spheres. Modified safranin stain, fluorescent microscopy, and antigen PCR improve detection.

Therapy

Disease self-limiting in immunocompetent. Otherwise, co-trimoxazole 160/800mg bd for 7d effective.

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[14] Chalmers RM & Davies AP (2010). *Exp Parasitol* **124**: 138–46.

Cystoisospora belli

First identified as human pathogen during World War I. Causes cholera-like symptoms in 1% of HIV-infected patients.

Clinical features

Almost indistinguishable from cryptosporidiosis, although peripheral eosinophilia can be feature (which no other coccidian elicits).[15] Rare in immunocompetent. Can be associated with acalculous cholecystitis in HIV patients.

Diagnosis

Stool microscopy. Acid-fast or modified safranin stains, fluorescent microscopy, and antigen PCR improve detection.

Therapy

Usually self-limiting, but sensitive to co-trimoxazole 160/800mg bd for 10d.

Coeliac disease

Disease involving abnormal small intestinal mucosa that usually heals when patients are treated with gluten-free diet, and relapses when gluten is reintroduced. First described by Samuel Glee in 1887, and attributed to gluten in 1941 by William Dicke.

Epidemiology and pathogenesis

- Prevalence through Europe ≈1:100; more common in Celtic populations. Also occurs in non-Caucasians but very rare in Black populations. ♀ slightly more commonly affected than ♂. Mortality ↓ by gluten-free diet, but remains higher than matched control population. Underdiagnosed.
- Disease phenotype produced in susceptible host by intestinal atrophy and inflammation due to T cell-mediated hypersensitivity reaction to component of gluten.
- Enterotoxicity produced by peptide corresponding to amino acids 31–49 of α-gliaden. 10–15% of 1st-degree relatives affected. Concordance rates for identical twins 70–100%. Strong association with HLA-DQ2 and HLA-DQ8; absence of these genes should trigger re-investigation for alternative diagnosis.

Clinical features

- Can present at any age. In children, classically occurs after weaning with failure to thrive, pallor, apathy, anorexia, and abdominal distension.
- In adults, most common age of presentation 20s-30s. Diarrhoea usually present, as are constitutional symptoms of lassitude, weight loss, glossitis, angular stomatitis, and symptoms of anaemia. Vitamin D deficiency or ➲ osteoporosis may be presenting problem.
- Other presentations in adults include depression and a Korsakoff-like syndrome. 30% of ♀ of childbearing age are amenorrhoeic. Men with untreated disease have low sperm counts and ↓ plasma testosterone levels.

[15] Legua P & Seas C (2013). *Curr Opin Infect Dis* **26**: 479–83.

- Although a bowel habit of 3–4 loose, pale, and often offensive stools is typical, normally formed stools do not preclude diagnosis, and bowel habit depends on gluten intake. Severe pain is not typical. Symptoms are often mild and non-specific. Given the prevalence, a high index of suspicion is appropriate, especially in patients with unexplained mild macrocytic anaemia with low serum ➲ folic acid.

Disease associations

- Link with organ-specific autoimmune diseases.
- Associated skin conditions include ➲ dermatitis herpetiformis, psoriasis, eczema, cutaneous vasculitis, epidermal necrolysis, and mycosis fungoides.
- 10–15% of coeliac patients have abnormal LFTs, and there is ↑ incidence of ➲ autoimmune hepatitis and ➲ primary biliary cholangitis.
- Association with ➲ inflammatory bowel disease, especially ulcerative proctitis. Microscopic colitis found in 4% of patients with coeliac disease, which represents a 70-fold ↑ in risk compared with the general population.[16] Such patients have relatively severe villous atrophy and frequently require glucocorticoids or immunosuppressive drugs to treat diarrhoea compared with patients with coeliac disease without microscopic colitis.
- Ulcerative jejunitis can be associated with coeliac disease and may be variant of a T cell proliferative condition that can result in T cell lymphoma.
- Rare associations include non-Hodgkin's lymphoma, gluten ataxia, and juvenile rheumatoid arthritis.
- Small minority of patients with coeliac disease have underlying ➲ immunoglobulin deficiency. Association with IgA deficiency probably mediated through defective clearance of gliadin antigen.

Investigations

- Blood tests may show anaemia, classically with iron or folate deficiency. Peripheral blood film may show target cells, Howell–Jolly bodies, acanthocytes, and thrombocytosis. Biochemistry may show ↓ calcium, vitamin D, zinc, and albumin.
- Useful **serological tests** include IgG and IgA antigliadin, and IgA antireticulin, antiendomysial and antitissue transglutaminase antibodies (most sensitive and specific).
- 0.5–1% of general population are IgA deficient, so important to exclude IgA deficiency as cause of false-negative serological testing; in such individuals IgG isotype autoantibodies should be tested.
- Small bowel biopsy remains essential. Four biopsies from 2nd part of duodenum using standard or jumbo-sized forceps are recommended (difficulty in interpretation sometimes occurs because of normal villous mucosa overlying Brunner's glands). In severe cases loss of normal duodenal circular fold pattern can be seen macroscopically, but this is not a reliable method of diagnosis.
- Radiology: barium follow-through can be abnormal, with loss of fine feathery mucosal pattern. Radiology important in presence of abdominal pain to exclude complicating jejunal stricture, lymphoma, or carcinoma. Abdominal CT may show splenic atrophy and associated low-grade adenopathy.

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[16] Green PH (2009). *Clin Gastroenterol Hepatol* **7**: 1210–6.

Treatment

- Gluten-free diet should avoid wheat, rye, and barley. Oats often avoided as products frequently prepared alongside other cereals so potential for cross-contamination. Supplementation with fibre may be needed. Repeat biopsy at 6mo necessary to assess response to diet. Further endoscopy after gluten challenge not indicated if patient responded well. Failure of response to diet usually (but not invariably) due to poor compliance or inadvertent ingestion of gluten. Refractory disease should only be diagnosed after strict adherence to an appropriate diet for 6–12mo. Type 1 refractory coeliac with normal T cell receptor γ type have lower risk of T cell lymphoma than Type 2. Rarely, failure to respond is due to small intestinal lymphoma or presence of another disorder (such as ➲ chronic pancreatitis). Gluten re-challenge rarely required.
- → CORTICOSTEROIDS reduce diarrhoea and facilitate weight gain, but effects do not persist after stopping drugs. Steroids may be useful in 10%, and 2nd line steroid-sparing agents such as → AZATHIOPRINE can be helpful in these patients longer term.
- There are several ongoing Phase 2 trials (for example, evaluating luminal gliadin binders or transglutaminase inhibitors), but none have yet borne fruit.

Complications

Most patients are lactose intolerant at time of diagnosis, but this rarely persists after treatment. Reported but poorly understood neurological complications including demyelination of posterior and lateral spinal cord columns and cerebellar degeneration which may respond, at least partly, to supplementation with vitamins A, E, and B, or calcium.

Collagenous colitis

See: ➲ Microscopic colitis.

Colonic cancer

Epidemiology and pathogenesis

As with other malignancies, colonic cancer is an acquired genetic disease produced by exposure to environmental carcinogens, with accumulations of damage over many years. In UK, ≈30,000 new cases, and 16,000 deaths, from colon cancer/y (figures for USA are 135,000 and 60,000). Rates lower in Japan and most developing countries. ➲ Rectal cancer different in epidemiology, pathogenesis, and treatment.

Adenoma-to-carcinoma hypothesis

Good epidemiological, clinical, pathological, and molecular evidence indicates that most colon cancers arise within previously benign adenomas. Cancer cells in malignant polyp share the same molecular alterations as in surrounding adenoma cells, but have additional mutations critical for malignant behaviour.

There are two general stages in colon carcinogenesis. Tumour initiation involves formation of an adenoma. All adenomas thought to arise from initial loss of *APC* gene function. Sporadic adenomas arise through acquired somatic mutations of both alleles; this takes years, so these polyps occur late in life and are relatively uncommon. In ➔ familial adenomatous polyposis (FAP), one *APC* allele is inherited in mutated form and the 2nd mutation takes much less time to acquire, so polyps occur at younger age—FAP is a disorder of tumour initiation. Progression to cancer is a consequence of the number of polyps rather than ↑ malignant potential of individual adenomas.

The second step involves progression from adenoma to carcinoma, termed tumour promotion. Involves mutations or deletions in tumour suppressor genes located on chromosomes 17 (p53) and 18 (deleted in colon cancer (*DCC*) gene). ➔ Hereditary non-polyposis cancer (HNPCC) is marked by accelerated tumour promotion stage. Adenomas progress more rapidly to cancer, which is why surveillance intervals in HNPCC need to be shortened.

Serrated polyp pathway

A smaller portion of colorectal cancers develop through serrated polyps, encompassing hyperplastic polyps, mixed hyperplastic adenomatous polyps, and serrated adenomas.

Risk factors

- Cancer family syndromes: ➔ familial adenomatous polyposis (FAP), ➔ Gardner's syndrome, ➔ HNPCC.
- Prior polyps. Main determinants of risk are polyp size >1cm and tubulovillous or severely dysplastic histology.
- Prior colon cancer (metachronous cancers in 5%).
- ➔ Inflammatory bowel disease. Main determinants of cancer risk: duration and extent of disease (~10% after 30y in patients with pancolitis).
- Diet. Risk modest. High fat and low fibre most common associations. High intake of red meat and highly refined starches and sugars also implicated.
- Smoking. Modest risk factor.

Clinical features

Change of bowel habit in people >40y is the classic symptom. Tumours often grow slowly and produce 1 of 4 main symptom patterns:

- **Obstruction**. Constipation, distension, pain, nausea, and vomiting. Obstruction is more common in the (narrower) sigmoid, descending, and transverse colon than in the caecum or ascending colon.
- **Bleeding**. Usually occult, presenting as iron deficiency anaemia. If visible, blood tends to be mixed in with stool.
- **Local invasion**. Often produces pain but can lead to ureteric obstruction, bladder invasion, or malignant fistulation.
- **Wasting syndrome**. Loss of appetite, weight, and strength. Can occur with any GI tract (and many other) malignancies. Particularly involves loss of subcutaneous fat.

Features of colon cancer in patients with inflammatory bowel disease show notable differences (tumours often synchronous, on background of chronic GI disease).

Investigations

- Colonoscopy most accurate and sensitive diagnostic modality (Plate 28). Even if distal tumours found, full colonoscopic evaluation required to detect synchronous lesions (5%, but more in IBD patients).
- CT pneumocolon (CT with air distension of the bowel) increasingly used and some centres are combining with PET. Labelling of intestinal contents with oral contrast media and removal of these from CT scans by digital image manipulation allows accurate radiological imaging of bowel without need for bowel cleansing. May have particular role in patients too frail to undergo colonoscopy.
- Barium enemas are still used, but biopsy not possible, patients find them unpleasant, and diagnostic sensitivity lower (≈85%).

Management

Key aim is to detect tumours early in their natural history and intervene with appropriate surgery. Management depends on staging (see ➲ Dukes staging and ➲ TNM classification).

Preoperative work-up

- CT chest, abdomen, and pelvis to identify metastases.
- Full colonoscopy to exclude synchronous colonic tumours.
- FBC, U&E, and (arguably) testing for ➢ CEA.

Local disease

- **Surgery** Curative. Local resection of tumour and regional nodes with clearance margins of 5cm is aim. Patients undergoing laparoscopic colectomy have faster recovery without worse recurrence or survival rates than with open colectomy. Tumours proximal to splenic flexure removed by right hemicolectomy; tumours of left colon removed by left hemicolectomy, and sigmoid cancers treated with low anterior resections (although very low tumours may require colostomy). Overall operative mortality for colorectal cancer ~5%. Treatment of ➲ rectal cancer covered elsewhere. Solitary liver metastases now constitute potentially resectable disease.
- **Adjuvant chemotherapy** after 'curative' surgery. Treating patients with Dukes stage C disease with 5-FU ± levamisole ↓ mortality by 30%; oral capecitabine appears equivalent. No survival benefit in stage B disease. Newer regimens including oxaliplatin and irinotecan being evaluated and may alter recommendations. Adjuvant radiotherapy for colon cancer outside rectum has no benefit.
- **Follow-up** 30% of patients undergoing 'curative' surgery develop metastases. Colonoscopy should be carried out 3–6mo postoperatively, and again at 12mo. Rise in ➢ CEA may indicate metastatic disease. Intensive follow-up with US or CT has minor impact, at considerable expense, on patient outcome.

Metastatic disease

- **Surgery** Single or small number of hepatic metastases should be considered for surgical resection because some patients will go on to experience prolonged disease-free interval. Solitary lung metastasis <3cm can also be considered for surgery, but impact on survival and cure rates less clear.
- **Chemotherapy** or **non-surgical ablation techniques** Intra-arterial infusion of chemotherapeutic agents reported to ablate or shrink a small number of tumours, with less systemic drug toxicity. Radiofrequency ablation using transcutaneously positioned needles may also be effective.
- **Biologics** Main advance in management of metastatic colorectal cancer in recent years has been addition of targeted therapy in the form of monoclonal antibodies. Bevacizumab (anti-VEGF) is licensed in combination with fluoropyrimidine-based chemotherapy as a 1st-line treatment. Cetuximab (anti-EGFR) approved for wild-type *KRAS* non-resectable liver-only metastatic disease.
- **Colonic stenting.** Up to 50% of patients presenting through casualty with colonic cancer do so with acute colonic obstruction. While primary surgery should be considered in patients with no evidence of metastatic disease, in those with metastases at presentation, endoscopic insertion of an uncovered self-expandable metal stent (SEMS) may be preferable. The UK ColoRectal Endoscopic Stenting Trial (CREST) also showed that stenting as a bridge to surgery ↓ stoma formation in patients who were appropriate for operative management if further preoperative work-up/optimization required.

Prognosis

Pathological stage (see ➔ Dukes staging) best predictor of outcome. Crude 5y survival rates (not adjusted for age-related mortality) are 85%, 65%, 40%, and <5% for stages A, B, C, and D, respectively. Relapse mostly occurs within 3y. Surveillance should be through combination of serum CEA (every 3–6mo for 3y, then every 6–12mo until 5y), CT annually for 3y, and colonoscopy 1y after surgery then every 3–5y.

Metastatic disease occurs in 25% and carries adverse prognosis. Mean survival period for patients with hepatic metastases (most common site) at diagnosis 4.5mo. Other metastatic sites include regional lymph nodes, lung, peritoneum, and adrenals. There is a suggestion that, with improving chemotherapy, the natural history is changing so that metastatic disease to lungs and brain, previously rarely seen, is becoming more common. CT most sensitive test for detecting occult metastases, and addition of PET scanning may further enhance early detection, particularly in patients with isolated liver or lung metastases.

Prevention of colonic cancer

- Diet. Current advice is to ↓ caloric intake, ↓ dietary fat to <25% of total calorie intake, enrich diet with 5 portions of fruit and vegetables/d, and include 25g/d fibre.
- Micronutrients. Theoretical benefits to calcium and selenium supplementation, not supported by clinical trials. Antioxidants, including vitamins A, E, and β-carotene, have not been proved to be beneficial or to ↓ rate of polyp recurrence.
- Aspirin and ➲ NSAIDs. Many (but not all) observational studies suggest aspirin and NSAIDs may ↑ survival in patients with early stage colorectal cancer. COX-2 inhibitors appear particularly protective, although additional clinical concerns regarding ↑ risk of GI bleed and cardiovascular morbidity. The non-steroidal sulindac ↓ polyp formation in ➲ familial adenomatous polyposis, but has shown conflicting results for sporadic colonic polyps.
- Statins. Despite early data suggesting statins ↓ cancer risk, more recent results suggest risk influenced by cholesterol levels.

Colonic polyps

Five common types (only adenomas are neoplastic):

- Adenomas.
- Benign hyperplastic polyps.
- Hamartomatous polyps.
- Inflammatory pseudopolyps.
- Submucosal (e.g. lipomas, leiomyomas, haemangiomas).

Adenomas

Can be pedunculated (Plate 27) or sessile, but very common (up to 50% in autopsy studies, frequency ↑ with age). Importance lies in risk of malignant transformation, which relates to size (adenoma >1cm has significant risk of containing cancer) and histology (can be tubular, villous (often sessile, more likely to contain focus of cancer), or tubulovillous).

Aetiology

Disordered and persistent cell replication coupled with retarded cell maturation. Genetic factors include aneuploidy, tetraploidy, and DNA hypomethylation. Altered expression of oncogenes *fos*, *myc*, *ras* occurs. Mutations in *APC*, *DCC*, *p53* reported. Environmental factors may include diet (some, but not conclusive, evidence for role of fat, fibre, bile acids, and faecal bacteria). NSAIDs may retard polyps in familial syndromes (➲ familial adenomatous polyposis (FAP), ➲ hereditary non-polyposis colon cancer (HNPCC)), but seem ineffectual in sporadic adenomas.

Clinical features

Usually asymptomatic. Rectal bleeding, prolapse, abdominal pain, or change in bowel habit usually occur with large polyps. No correlation with histology or location. Only polyps >1.5cm associated with positive faecal occult blood tests. Large villous adenomas can produce high-volume watery diarrhoea and hypokalaemia (McKittrick-Wheelock syndrome).

Diagnosis

Endoscopy (sigmoidoscopy/colonoscopy), CT colonography, or barium radiology. Endoscopy currently most sensitive, and only modality that allows biopsy and therapeutic excision. Kudo pit pattern (Plates 29-34) predicts risk of neoplasia.

Natural history

Adenoma–carcinoma progression probably takes 7–10y, possibly less in the case of HNPCC/microsatellite instability. Although polyps grow slowly, and perhaps ≤5% destined for malignancy, necessity of excision for histology underlies current advice that all colonic polyps should be removed if possible.

Management

See ➲ polypectomy.

Benign hyperplastic polyps

Usually <5mm, often multiple, most common in rectosigmoid. ≈50% of all polyps <5mm are hyperplastic. Arise because of ↑ number of epithelial cells per unit length, which causes buckling and serrated surface. Small distal hyperplastic polyps almost never turn malignant. However, large, more proximal hyperplastic polyps may be precursors to sessile serrated polyps, which have malignant potential (Box 4.12).

Hamartomatous polyps

An abnormal mixture of benign cells. See ➲ juvenile polyps, ➲ Peutz–Jeghers, and ➲ Cowden's disease.

Inflammatory pseudopolyps

Pseudopolyps are common in ➲ ulcerative colitis, but also seen in ➲ Crohn's, infective, and ischaemic colitis. Represent islands of residual mucosa in a sea of previously sloughed healed mucosa.

Box 4.12 When is a colonic polyp not a polyp?

'Polyp' means any tissue protrusion above a mucosal surface into the lumen.

Neoplastic polyps
(Adenomas and cancers): see text.

Non-neoplastic polyps
Hyperplastic, inflammatory, hamartomatous (with caveats as per text).

Other lesions

- Lipomas, fibromas, leiomyomas, and ➲ Kaposi's sarcoma usually submucosal and less often diagnosed by biopsy.
- Pneumatosis can appear polypoid.
- Angiomas can sometimes be sampled by hot biopsy but risk of bleeding.
- Benign lymphoid nodules can be mistaken for neoplasms or polyps, especially in terminal ileum.
- Occasionally metastatic tumours may be seen on colonoscopy.
- ➲ Carcinoid.

Colonic transit studies

See: ▹ 'Colonic transit studies', p. 157.

Constipation

See: ▶ Approach to constipation.

Cowden's disease

Autosomal dominant condition presenting with multiple hamartomas of skin and mucus membranes. Incidence 1/200,000 (though likely underdiagnosed). Caused by mutations in *PTEN*. Hallmark is multiple trichilemmomas around eyes, nose, and mouth. Oral papillomas common (Plate 7), and up to 80% have hamartomas scattered throughout GI tract. These can be 1mm to several centimetres in diameter and include lipomas, juvenile polyps, inflammatory polyps, ganglioneuromas, and lymphoid hyperplasia. Glycogenic acanthosis frequently seen in oesophageal lesions. Lifetime risk of colon cancer 9%, hence 2-yearly screening colonoscopy advocated. Risk of other cancers also increased, including breast (85%), thyroid (35%), endometrium (28%), renal (34%) and melanoma (6%).[17] See also ➲ juvenile polyposis.

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[17] Tan MH *et al.* (2012). *Clin Cancer Res* **18**: 400–7.

COX-1 and COX-2

See: ➲ Non-steroidal anti-inflammatory drugs (NSAIDs) and the GI tract.

Crohn's disease

Named after Burrill Crohn, a New York physician who published in 1932 on 'regional ileitis' with Ginsberg and Oppenheimer, but first described by Dalziel in 1912. Chronic inflammatory condition that can affect any part of gut, from mouth to anus, but most frequently distal small intestine and colon.

Epidemiology

- Accurate figures difficult because of lack of gold standard diagnostic criteria and global variations in case ascertainment.
- Found worldwide, but incidence varies: 4–8/100,000 in UK, USA, and N. Europe; 2/100,000 in Australasia and S. Africa; and 0.05–0.8/100,000 in Asia and S. America. Incidence ↑ 6-fold from 1950s to 1980s, but appears to have stabilized since.
- Slightly more common in ♀. Peak onset between age 20–40, with 2nd smaller peak in older adults.

Aetiology and pathogenesis

- Almost 100 years after initial description, whether Crohn's disease represents an appropriate response to an unrecognized pathogen, or an inappropriate response to innocuous stimuli is not fully resolved.
- Resemblance to some animal diseases with known bacterial cause (Johne's disease in goats), and proven role of gut pathogens in inducing inflammation in genetically susceptible animal models of IBD, strongly suggest central role for bacteria as triggering factors.
- Huge amount of experimental work has helped define the cellular and humoral immune events underlying mucosal inflammation. Some evidence of over-responsiveness of T cells to enteric flora, with T cells producing a Th1 cytokine response profile in Crohn's disease.
- Strong genetic component, with high concordance among monozygotic twins, and ↑ incidence among Ashkenazi Jews. Genome-wide association studies have identified >140 susceptibility loci.
- Recent evidence also highlights importance of defects in innate immune response in pathogenesis of Crohn's disease, including:
  - Macrophages have impaired cytokine secretion after bacterial exposure, with ↓ neutrophil recruitment and microbial clearance.[18]
  - Discovery of susceptibility genes including the *CARD15* pathogen receptor (senses bacterial muramyl dipeptide), autophagy genes *ATG16L1* and *IRGM*, and the IL-23 receptor).[19]
  - ↓ Epithelial integrity.

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[18] Smith AM *et al.* (2009). *J Exp Med* **206**: 1883–97.

[19] McGovern DP *et al.* (2015). *Gastroenterology* **149**: 1163–76.

  - Dysregulation of antimicrobial peptides, especially α-defensin produced by Paneth cells at base of intestinal crypts.
  - Increasing evidence that the IL-12/IL-23—Th-1/Th-17 axis is key to interaction between innate and acquired immune responses in Crohn's pathogenesis.
- Genetic diseases involving defects in bacterial killing and degradation (e.g. ➲ chronic granulomatous disease) produce GI phenotype very similar to idiopathic Crohn's disease.
- Recent ↑ in incidence supports importance of environmental factors. Diet and smoking particularly important. Some evidence suggests Crohn's patients have problem handling saturated fats, while smoking worsens disease possibly because of effect on microvasculature.

Pathology

Hallmark is focal intestinal inflammation. Disease classically discontinuous, giving rise to 'skip lesions' (unlike UC, which is continuous). Early lesions include aphthous ulcers overlying lymphoid aggregates, and support role of luminal antigens initiating immune activation. Non-caseating granulomas found in up to 70% of surgical resection specimens. Inflammation is transmural, which accounts for development of large ulcers, sinus tracks, fissures, and fistulae. Concomitant attempts at healing lead to extensive fibrosis as a major component of Crohn's disease.

Clinical features (see Plate 23 and 24)

Disease distribution

40% have disease confined to terminal ileum and caecum, 20% to colon, and 30% have ileocolonic disease. Remaining 10% have disease elsewhere in GI tract, particularly perianal disease, although mouth, oesophagus, and stomach can also be affected.

Symptoms

Classic symptoms are **abdominal pain** and **diarrhoea**. Weight loss, anorexia, and fever may be seen. Growth retardation common and important in children. Rectal bleeding/acute haemorrhage uncommon.

- **Anaemia** occurs in 30%, mainly as result of iron deficiency but sometimes due to ➲ vitamin B_{12} deficiency in ileal disease or ➲ folate deficiency in proximal small bowel disease.
- Patients can present with small bowel **obstruction** or symptoms relating to **stricturing**.
- Colonic Crohn's disease may present with bloody diarrhoea, but tenesmus less common than in ➲ ulcerative colitis because rectum less commonly affected (although ~30% of patients with ileal disease have some degree of proctitis).
- Gastroduodenal Crohn's disease can present as *Helicobacter*-negative peptic ulcer disease.

Extraintestinal manifestations

- Pauci-articular arthropathy affects 6%, usually accompanying active intestinal disease and may include sacroiliitis. Large joints predominantly affected. Association with ankylosing spondylitis in patients who are HLA-B27^{+}.
- **Metabolic bone disease** common: osteopaenia (T score on ➤ DEXA scan: –1 to –2.49) in up to 50%. Steroid usage is main risk factor, but loss of bone density is an independent feature of disease.
- Association with venous and arterial **thromboembolic disease**. Hospitalization, immobility, and malnutrition contribute, but in addition platelets can be high and many clotting factors are increased. Treatment with prophylactic anticoagulants safe and effective.
- Mucocutaneous manifestations include aphthous ulceration, ➲ pyoderma gangrenosum, and ➲ erythema nodosum, typically varying with disease activity.
- Ocular manifestations (scleritis, episcleritis, and anterior uveitis) occur in ≈5%.
- ➲ Gallstones twice as common than in control populations. Association with ➲ fatty liver ➲ autoimmune hepatitis and ➲ primary sclerosing cholangitis.
- Terminal ileal disease associated with renal ➲ oxalate stones.

Disease behaviour

Can be inflammatory, stricturing, or penetrating. This has been incorporated into Montreal classification (Table 4.10). Fistulae reflect transmural character of Crohn's disease. Perianal fistulae occur in 15–30%; enteroenteric, enterovaginal, and enterocutaneous fistulas can also arise.

Table 4.10 Montreal classification for Crohn's disease

Feature	Classification	Definition	Notes
Age at diagnosis	A1 A2 A3	≤16y 17–40y >40 years	Time of histological, surgical, radiological, or endoscopic diagnosis No retrospective time of diagnosis
Location	L1 L2 L3 L4	Ileal Colonic Ileocolonic Isolated upper GI disease[*]	Maximum extent of lesions at any time before resection Aphthous lesions or ulcerations of any size (mucosal erythema not enough)
Behaviour	B1 B2 B3 p	Inflammatory Stricturing Penetrating Perianal disease modifier[†]	Inflammatory masses, abscesses, fistulae and perianal ulcers defined as penetrating Strictures can be diagnosed radiologically, endoscopically, or surgically Postoperative complications are excluded

[*] L4 is modifier that can be added to L1–L3 when concomitant upper GI disease present.[†] p' added to B1–B3 when concomitant perianal disease present.

Establishing diagnosis and evaluating disease

History and examination

Focus on recent travel, antibiotic use, diet, family history, and sexual activity. Ask about smoking. Examine for signs of obstruction, tenderness, or mass. Always examine perianal region.

Laboratory tests

- Blood tests:
  - FBC. Look for anaemia, ↑ WBC, ↑ platelets.
  - Haematinics (including iron, TIBC, B_{12}, and folate).
  - LFTs. Liver often switches off synthesizing albumin and into making acute phase reactants such as CRP.
  - Look for vitamin **and** micronutrient deficiency: calcium and magnesium levels can be low, and zinc may be deficient in extensive small bowel disease (and is critical for tissue healing).
- Stool tests:
  - MC&S, OCP, and ➲ *Clostridioides difficile* toxin.
  - ▸ Faecal calprotectin (see p. 151) has high sensitivity for differentiating between IBD and functional GI disorders.
- Endoscopy:
  - Colonoscopy standard for diagnosing colonic and terminal ileal disease. Only modality that permits mucosal biopsy, and also allows for balloon dilatation of any strictures.
  - ▸ Video capsule endoscopy can be used to visualize small bowel and can detect lesions not visible in other modalities. Risk of obstruction in patients with strictures, so patency capsule first.
- Imaging:
  - Barium follow-through was standard method for evaluating small bowel, but largely superseded by US, CT, and MRI.
  - US (particularly of small bowel) very useful in expert hands. High sensitivity and specificity for detecting thickened bowel (particularly terminal ileum), abscesses, and fistulae.
  - Standard CT does not show mucosal detail but very helpful in discerning extraluminal features, and mural thickening. CT (with barium), or ▸ CT enterography (p. 589) useful in evaluating small bowel disease. Bear in mind radiation exposure, particularly in young patients who may have many scans over their lifetime, but usually modality of choice in emergencies due to availability.
  - MRI enterography has similar accuracy to CT for disease location and wall thickening, and better for detecting strictures.

Differentiating Crohn's disease from ulcerative colitis

Can be an issue when IBD confined to colon. Discriminating features include small bowel or mainly right-sided colonic disease, rectal sparing, fistulization, perianal disease, and granulomas, all of which favour Crohn's disease. Immunological markers may help: pANCA found in 70% of UC but only 15% of Crohn's patients, and antibodies to *Saccharomyces cervisiae* (ASCA) found in up to 50% of Crohn's patients (less often in UC). When combined, specificity further improved.

Assessing disease activity

Usually sufficient to follow patient's response to treatment, as well as simple markers of inflammatory activity such as CRP. There are a number of scoring systems that are important research tools: see ➲ Crohn's disease activity indices.

Aims and principles of management

Since cure not available, goal is to induce and maintain remission.

- → CORTICOSTEROIDS still play central role in management of Crohn's disease, although do not heal the disease and adverse side effects well known. Useful for rapidly inducing remission, but not effective as long-term therapy (although many patients find difficulty in tapering dose without recurrent symptoms). Budesonide almost as effective as prednisolone, with fewer side effects.
- Thiopurines (→ AZATHIOPRINE or → MERCAPTOPURINE), and → METHOTREXATE widely used in patients with active Crohn's disease who fail to respond to 1st-line therapies, or who fail to taper steroids. Generally require several weeks for activity to become apparent. Data on → CICLOSPORIN and mycophenolate do not indicate major role for these drugs in Crohn's disease.
- → AMINOSALICYLATES widely used, but little evidence superior to placebo, and most guidelines now recommend against. Some evidence for mesalazine in treating colonic disease, but by no means definitive.
- Increasing numbers of biologics now available (see Box 4.13):
  - → ANTI-TNF antibodies. Infliximab, adalimumab, and their biosimilars (see Box 4.14) of proven efficacy. The TNF receptor analogue etanercept is ineffective.
  - Anti-integrin therapy. Natalizumab effective in Phase 3 trials but has been withdrawn (not gut selective; risk of JC virus reactivation). → VEDOLIZUMAB ($\alpha_4\beta_7$; gut selective) licensed.
  - Anti-IL-12/IL-23 therapy with → USTEKINUMAB approved.
  - Other novel oral therapies (e.g. selective JAK inhibitors and S1P modulators) currently in trials.
- Antibiotics:
  - → METRONIDAZOLE reduces post-surgical endoscopic recurrence after ileal resection, and probably also heals perianal fistulae. May not be totally due to antibacterial properties since *in vitro* inhibits neutrophil margination across endothelium. ❗ Can cause irreversible peripheral neuropathy with extended use.
  - → CIPROFLOXACIN also used in treating complications of Crohn's disease with good effect.
- Claims made for multiple antibacterial therapies targeted against mycobacteria. Most trials have been equivocal: recent Cochrane review 🖱 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000299.pub3/abstract;jsessionid=C61747997C8DD76D3EE71A2829847D32.f02t02 mildly supportive, but not recommended at time of writing.
- Nutritional therapy targets both repletion of specific nutrient deficits and primary therapy of disease. ➲ Elemental diets as effective as corticosteroids in inducing remission, particularly in children, but unpalatable.

Surgery

- 75% of Crohn's patients will have surgery within 20y of diagnosis. Indications include complications such as intra-abdominal masses, medically intractable fistulae, fibrotic strictures with obstruction, toxic megacolon, haemorrhage, and cancer.
- Diversion of faecal stream by creating proximal defunctioning ileostomy or colostomy effective for treating distal inflammation in recalcitrant disease.
- Details of surgical procedures vary with site of disease, and to some extent with country, but can be classified as follows:
  - Resections with or without anastomoses.
  - External or internal bypass surgery.
  - Surgical procedures to repair or resect fistulae.
- Recurrent disease common after surgery and has been assessed endoscopically as approaching 80% at 12mo. Often said that ≈50% of patients undergoing surgery will need another operation within 10y, but these are figures from pre-biologics era.

❗ Practice point: Thiopurine prescribing and monitoring

See also ➤ therapeutic drug monitoring in IBD.

Before prescribing

- Screen for HBV, HCV, HIV, VZV, and EBV.
- CXR
- Measure ➔ thiopurine methyltransferase (TPMT) activity (genotype and enzyme level activity).

Initial dosing

Adjust dose according to TPMT level:

- Zero: Avoid thiopurine. Consider other treatment.
- Heterozygote: AZA: 1–1.25mg/kg/d; 6-MP: 0.5–0.75mg/kg/d.
- Normal: AZA: 2–2.5mg/kg/d: 6-MP 1–1.5mg/kg/d.

Monitoring

- FBC and LFTs at 2, 4, 8, 12 wk, and 3-monthly thereafter.
- Levels of metabolites of pathway can be used to identify non-adherent or underdosed patients. Measure at Wk 4, 12, and annually, and 4 wk after any dose change or if not responding:
  - 6-TGN = 230–400 increases likelihood of clinical effect.
  - 6-MMP>5,000 increases likelihood of hepatotoxicity.

Role of allopurinol

Allopurinol causes shunting of metabolites away from 6-MMP, resulting in ↑ 6-TGN levels. Precise mechanism unknown, and further studies required to establish dosing and clinical safety. However, one regime is to prescribe 100mg allopurinol while reducing dose of thiopurine by 75%.

Vaccines

Give pneumococcal vaccine before commencing treatment, and influenza vaccine annually. Avoid live vaccines.

Crohn's disease in pregnancy

Active disease associated with ↓ fertility, which may relate to chronic inflammation, undernutrition, or ↓ libido. Women with quiescent disease at conception have same rate of recurrence as non-pregnant women. Among those with active disease at conception, ⅓ improve, ⅓ become worse, and ⅓ do not change during pregnancy. Most pregnancies normal, and perianal complications develop infrequently in women who deliver vaginally with an episiotomy. Risks of adverse outcomes in pregnancy in ♀ with quiescent disease similar to healthy women. However, active disease associated with ↑ incidents of preterm birth rates, low birth weights, and ↑ caesarean section rates.

Box 4.13 Biologic therapy in Crohn's disease

- Infliximab is a murine chimaeric antibody to TNF, administered IV, which induces and maintains response in moderately severe and fistulating Crohn's disease, ↓ need for steroids, induces and maintains mucosal healing, ↓ hospitalization and surgery rates, and improves quality of life. Response rates ~70%, with remission rates at 12mo ≈35%. About 10—15% lose response per year.
- Adalimumab is an IgG_1 fully humanized monoclonal antibody, given SC, and has comparable efficacy to infliximab.
- Episodic usage of anti-TNFs has been widely eschewed, partly because of higher anti-drug antibody titres and infusion reactions in episodically treated patients.
- Concurrent administration of azathioprine and infliximab shown in SONIC study to be superior to treatment with either alone, although ↑ adverse events (particularly infection).[20]
- Up to 50% of patients lose response to, or become intolerant of, anti-TNFs (secondary non-responders). Response can be recaptured by ↑ dose or ↓ interval between doses (e.g. in case of, infliximab, ↑ dose from 5 to 10mg/kg), or by switching to alternative anti-TNF. More recently tests becoming available that allow drug and antibody monitoring, which distinguish those patients who will benefit from dose escalation and those who will not (see also ⊳ therapeutic drug monitoring in IBD). Also some evidence that co-administration of immunosuppressants may confer additional benefit in terms of preventing immunogenicity.
- Newer, non-anti-TNF agents may be used in refractory patients who have failed anti-TNF therapy. These include → VEDOLIZUMAB and → USTEKINUMAB. These may move ahead in treatment paradigm as experience grows and price falls.
- Whether to use biological therapy early in course of disease ('top down') or maintain more traditional escalation via steroids and immunosuppressants ('bottom up') is subject of active debate, although there is a general move towards earlier use of biologic therapies. ≈50% of Crohn's patients will not follow aggressive course, but predictors of IBD natural history still have to be identified.

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[20] Slavik T & Montgomery EA (2014). *J Clin Pathol* **67**: 891–7.

Safety of drugs used in Crohn's disease in pregnancy

Only drug unequivocally contraindicated in pregnancy is → METHOTREXATE. Aminosalicylates and steroids are safe, and most authorities now advise continuation of azathioprine/mercaptopurine, even for planned pregnancies. Increasing evidence that anti-TNFs are safe. A large study (PIANO) of 1,000 women with IBD found no ↑ in 'any pregnancy complications', and normal developmental milestones up until 12mo of age. The only finding was of ↑ infant infections at 12mo, and longer term data are awaited. Both infliximab and adalimumab cross placenta in 3rd trimester, and therefore are generally withheld at this time if possible. Also, the baby should not receive live vaccines until 6mo post-partum.

Box 4.14 Biosimilars

Biosimilars are drugs that do not have a clinically meaningful difference to other biologic medicines. Recently, a number of such drugs have been licensed in IBD. Biosimilars have inherent structural differences, and are therefore not generic equivalents, and their efficacy needs to be proven in trials. Current BSG guidance advises that infliximab should be prescribed by its brand name (e.g. Remicade®, Remsima®, or Inflectra®). While automatic substitution is not appropriate, there is sufficient evidence to recommend that patients who are in stable clinical response or remission on Remicade® can be switched to Remsima® or Inflectra® at the same dose and dosing interval. This should be done after discussion with patient.

Course and prognosis

Rate of relapse in first 1–2y correlates with risk of relapse in ensuing 5y. ≈25% of patients will maintain long periods of remission, 25% experience chronically active symptoms, and 50% have course that fluctuates between active and inactive disease.

Risk of cancer

When Crohn's disease affects colon, risk of ➲ colon cancer parallels that in ➲ ulcerative colitis. Surveillance colonoscopy recommended from 10y after diagnosis. Data from radiological studies in 1970s suggest stricturing disease of colon has higher risk of malignancy (≈7%). There is ↑ risk of small bowel adenocarcinoma in small bowel Crohn's disease, and probably small ↑ risk of Hodgkin's and non-Hodgkin's lymphomas.

Crohn's disease activity indices

Symptoms and clinical signs of Crohn's disease do not always correlate with inflammatory severity. Cardinal features of abdominal pain and diarrhoea may be due to superimposed ➔ irritable bowel syndrome, previous surgical resection, or complications such as strictures or fistulae.

Most widely used activity index is **Crohn's disease activity index (CDAI)** (Box 4.15). Main criticisms are excessive weight put on number of bowel actions/d, which can be influenced by many factors apart from disease activity, and inclusion of haematocrit as marker of activity. Many research studies use fall in CDAI as primary endpoint of efficacy. The following scores are practical for clinical practice:

- Asymptomatic remission: CDAI <150. ❗ Note: if patient requires steroids to remain asymptomatic, they are classed as 'steroid-dependent', not 'in remission'.
- Mild-to-moderate disease: CDAI 150–220.
- Moderate-to-severe disease: CDAI 220–450.
- Severe-fulminant disease: CDAI >450.
- Clinical response: ↓ in CDAI by >70 points.

The **Harvey–Bradshaw index** is a simplified form of the CDAI and also in widespread use in research studies. Score <4 corresponds to CDAI <150 (clinical remission), and 3 point ↓ to decrease in CDAI of 100 points.

Endoscopic activity scores such as the **Crohn's disease endoscopic inflammation score** (CDEIS) or **Rutgeerts Score** (for postoperative recurrence) are also widely used (Box 4.16).

Box 4.15 Calculating Crohn's disease activity index

$$\text{CDAI} = 2 \times \mathbf{1} + 5 \times \mathbf{2} + 7 \times \mathbf{3} + 20 \times \mathbf{4} + 30 \times \mathbf{5} + 10 \times \mathbf{6} + 6 \times \mathbf{7} + \mathbf{8}$$

where

1 = Number of liquid or very soft stools in 1wk.

2 = Sum of 7 daily abdominal pain ratings: (0 = none, 1 = mild, 2 = moderate, 3 = severe).

3 = Sum of 7 daily ratings of general well-being: (0 = well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible).

4 **=** Symptoms or findings presumed related to Crohn's disease (score 1 for each):

- Arthritis or arthralgia.
- Iritis or uveitis.
- Erythema nodosum, pyoderma gangrenosum, aphthous stomatitis.
- Anal fissure, fistula, or peri-rectal abscess.
- Other bowel-related fistula.
- Febrile (fever) episode over 100°F during past week.

5 = Taking Lomotil or opiates for diarrhoea.

6 = Abdominal mass (0 = none; 0.4 = questionable; 1 = present).

7 = Haematocrit [(typical – current) × 6]; normal average: ♂ = 47; ♀ = 42.

8 **=** Weight factor: 100 × [(standard weight – actual body weight)/standard weight].

Online calculator 🖱 http://www.ibdjohn.com/cdai/ available.

Box 4.16 Rutgeerts score

- Grade 0: No lesions in distal ileum.
- Grade 1: ≤5 aphthous lesions.
- Grade 2: >5 aphthous lesions with normal mucosa between lesions, or skip areas of larger lesions confined to ileocolonic anastomosis (that is, <1cm in length).
- Grade 3: Diffuse aphthous ileitis with diffusely inflamed mucosa.
- Grade 4: Diffuse ulceration with already larger ulcers, nodules, and/or narrowing.

Cronkhite–Canada syndrome

First reported in 1955. Non-inherited syndrome. Occurs in middle-aged and older people. ≈⅔ of Japanese descent. Aetiology unknown, but may be IgG4-related disease. Consists of diffuse GI hamartomatous polyposis, dystrophic fingernails, alopecia, cutaneous hyperpigmentation, dysgeusia, and ➲ protein-losing enteropathy.[21]

Treatment challenging. Involves nutritional support and corticosteroids acutely, substituted with → AZATHIOPRINE for long-term maintenance. ➲ Bacterial overgrowth can complicate. Prognosis poor (mortality 50%, usually due to GI bleeding, malnutrition, or infection). Cancer arises in 15% so regular endoscopic surveillance recommended, although optimum interval not defined. Total gastrectomy or panproctocolectomy advocated if dysplasia identified.

Cyclical vomiting syndrome

Chronic functional disorder, principally affecting children but can persist into adolescence and adulthood. Slight predominance in ♀ > ♂.

Clinical features

- Sudden, repeated attacks of nausea and vomiting, which can last hours to days. Patients rapidly become fatigued, dehydrated, and can suffer metabolic imbalance as consequence.
- Important in the history to identifying triggers, such as food and menstrual cycle, which may help with management of symptoms.
- Also exclude drug causes of emesis, including cannabis.

Investigation

- Diagnosis of exclusion.
- Primary investigations should focus on establishing extent of dehydration and electrolyte imbalance.
- Subsequently, purpose of investigations should be to exclude central and autonomic nervous system causes of vomiting, and peripheral causes such as GI dysmotility. Usually completed with cross-sectional imaging and dynamic testing (such as motility studies and autonomic testing).

[21] Colombel JF *et al.* (2010). *N Engl J Med* **362**: 1383–95.

Management

- Initially aim to replace fluid and electrolyte losses (often needs to be performed IV). Provide regular → ANTIEMETICS.
- During prodrome phase of nausea, medication to ↓ acid production may be of value, as can judicious use of benzodiazepines.
- If associated with migraine, sumatriptan may be of use.
- No specific preventative measures, but aim for adequate sleep**,** stress reduction, and elimination of as many triggers as possible.
- Above all, sympathetic approach to these patients required, and may in its own right confer therapeutic benefit.

Cryptosporidium

See: ➲ Coccidia.

Cyclospora

See: ➲ Coccidia.

Cystic fibrosis (CF) and the GI tract

Epidemiology and pathogenesis

Autosomal recessive. Prevalence: 1/3,000 in northern Europeans, with gene carriage in 1/25. Results from mutations in gene for the cystic fibrosis transmembrane conductance regulator (*CFTR*), a cAMP-activated chloride channel found in secretory epithelia. Major complications of pulmonary and GI system because of production of dehydrated protein-rich secretions (Box 4.17).

Clinical features

- GI complications increasingly common, due in part to improved management of pulmonary complications and ↑ life expectancy (median 30y).
- Most common cause of exocrine ➲ pancreatic insufficiency in childhood (90–95% of children with CF). Severity of pancreatic disease parallels lung involvement. Presents with failure to thrive, steatorrhoea, and colicky abdominal pain. Predisposes to malabsorption of fat-soluble ➲ vitamins A, D, E, and K. Diabetes mellitus in 8–12% of patients >25y.
- Bile duct plugging due to secretions may lead to indolent development of secondary biliary cirrhosis and ➲ portal hypertension. Hepatic congestion due to pulmonary hypertension/right heart failure. ➲ Fatty liver in 20%; ➲ gallstones in 15% of young adults.
- May result in meconium ileus at birth (12% of neonates) and distal intestinal obstruction syndrome (DIOS) later. Intestinal obstruction, intussusception, and rectal prolapse may occur. Excessive → PANCREATIC ENZYME SUPPLEMENTS in children associated with colonic strictures (fibrosing colonopathy).

- ➲ Gastro-oesophageal reflux disease more common, although aetiology unclear. Hypothesized to contribute to chronic lung disease (micro-aspiration and airway inflammation), so many patients treated with → PROTON PUMP INHIBITORS.
- ➲ Bacterial overgrowth occurs commonly due to recurrent treatment with antibiotics and bowel dysmotility. Probiotic use encouraged, with cyclical antibiotics (no standard strategy) if required.

Investigations

- Diagnosis usually made in infancy, based on typical pulmonary and GI tract manifestations, family history, and positive results on sweat test. Confirmation by genetic testing in most cases.
- Investigation of GI complications depends on specific presentation.
- Check vitamin A, D, E, and K levels.

Management

- Multidisciplinary approach to care, with expert nutritional support. Replace ➲ vitamin deficiencies.
- → PANCREATIC ENZYME SUPPLEMENTS for exocrine insufficiency.
- Lung and ➲ liver transplantation have been successful.
- Gene therapy remains ultimate goal for treatment of CF.

Box 4.17 CF mutations and pancreatitis

Recent observations suggest heterozygosity for *CFTR* may be linked to recurrent ➲ acute pancreatitis and idiopathic ➲ chronic pancreatitis. Few of these patients have any evidence of pulmonary disease or abnormal sweat tests. Mutations within CFTR have also been associated with ↑ risk of pancreatic adenocarcinoma, independent of pre-existing pancreatic disease.

Cytomegalovirus (CMV)

50–80% of the population are seropositive for CMV. Primary infection in immunocompetent hosts causes few or no symptoms, and can mimic glandular fever. Immunosuppression can lead to CMV retinitis, pneumonitis, colitis, and oesophagitis. CMV is 3rd most common pathogen in AIDS after *Pneumocystis* and ➔ *Candida* (see ➔ HIV and the gut).

CMV colitis

Occurs in 2–15 % of patients with solid organ transplants (average 5–7mo after transplant) and 3–5% patients with HIV/AIDS. Rare in immunocompetent hosts but can complicate ➔ ulcerative colitis, especially in patients receiving steroids. Patients with steroid-dependent colitis who present with refractory disease should be assessed for CMV infection. Suspect CMV in patients presenting with apparent flare who initially improve with immunosuppression but subsequently deteriorate.

Diagnosis

Sigmoidoscopy or colonoscopy allows mucosal visualization and biopsy. Histology may reveal inclusion bodies and immunohistochemistry may show CMV antigen. Distribution can be patchy, so multiple biopsies with examination of all tissue levels important.

CMV oesophagitis (Plate 14)

Unknown in healthy hosts. Found in 10–25% patients with AIDS undergoing upper GI endoscopy. Symptoms include odynophagia, nausea, vomiting, fever, diarrhoea, weight loss, and chest pain. Diagnosis usually involves upper GI endoscopy and biopsy: appearances classically of large shallow ulcers.

Therapy

→ GANCICLOVIR 5mg/kg IV bd for 2–3wk.

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Dentate line

Represents border between distal squamous mucosa and transitional area of squamous/non-squamous mucosa within anal canal (Fig. 4.7). Usually located in middle portion of internal anal sphincter; 4–8 anal glands drain into columns of Morgagni at this level, and most rectal abscesses and fistulae originate in these glands. Also delineates where sensory fibres end. Proximal to this line, rectum supplied by stretch, but not pain, nerve fibres (allowing endoscopic biopsies and surgical procedures to be performed without anaesthesia above this point).

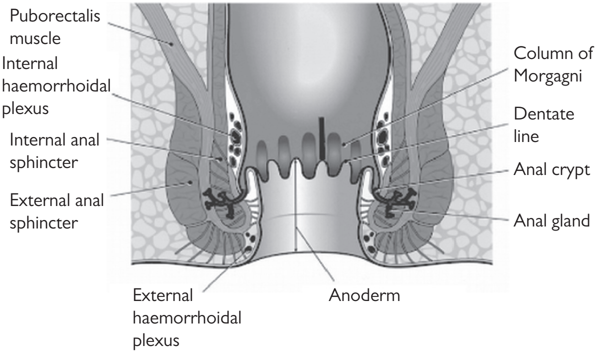
Puborectalis muscle
Internal haemorrhoidal plexus
Internal anal sphincter
External anal sphincter
Column of Morgagni
Dentate line
Anal crypt
Anal gland
External haemorrhoidal plexus
Anoderm

Fig. 4.7 Anatomy of anal canal. The heavy vertical line denotes the transition zone 1–1.5cm proximal to the dentate line.

Dermatitis herpetiformis

Itchy, papulovesicular eruption, symmetrical on elbows, buttocks, knees, sacrum, face, neck, and trunk (see Plate 43). Very closely associated with ➔ coeliac disease - nearly 100% have abnormal jejunal mucosa. Characterized by IgA deposition at dermo-epidermal junction away from sites of blistering. Pathogenesis unknown.

Treatment

- All patients should adopt gluten-free diet.
- Dapsone 1–2mg/kg effective.
- Sulfapyridine may be used as 2nd-line therapy.

Dermatomyositis

- Acquired muscle disease, with autoimmune basis, characterized by proximal muscle weakness, endomysial inflammation, and ↑ serum muscle enzymes (e.g. creatine kinase, AST, LDH). Other features include heliotrope (purplish-blue) rash around eyes, , Raynaud's phenomenon, photosensitive poikilodermic shawl distribution rash, and Gottron's papules on hands.
- GI involvement includes:
  - Dysphagia, due to striated muscle involvement in upper ⅓ of oesophagus (15–50% of cases).
  - Ulcers and bleeding.
  - Vasculitis with abdominal pain and bowel infarction.
  - ➲ Acute pancreatitis (rare);
  - Association with internal malignancy in 10–20%.
- Diagnosis made on basis of clinical history, ↑ serum muscle enzymes, antinuclear antibodies (80%), myositis-specific antibodies (e.g. anti-Jo1), needle EMG showing myopathic features with indications of muscle irritability, and muscle biopsy (often guided by MRI) findings of inflammation and perifascicular atrophy.
- Oesophageal involvement may be demonstrated by manometry (see ➲ oesophageal motility disorders).
- Important to screen for underlying malignancy.
- Management includes immunosuppression with steroids.

Diabetes and the GI tract

Altered gut motility

Due to ➲ autonomic neuropathy. Can result in:

- Oesophageal dysmotility. Secondary ➲ gastro-oesophageal reflux disease is common, as is oesophageal ➲ candidiasis with chronic poor glycaemic control.
- Diabetic gastroparesis.
  - Delayed gastric emptying on scintigraphy found in up to 50% of unselected patients, with impaired proximal relaxation after meals and antral hypomotility. ~25% of insulin-dependent diabetics with peripheral neuropathy report nausea, vomiting, early satiety, bloating, and heartburn, although correlation between symptoms and demonstrable gastroparesis is weak.
  - Suspect diagnosis in patients with consistent symptoms and negative endoscopy or barium study.
  - Pathophysiology complex and may involve impaired visceral sensation, gastric smooth muscle degeneration, local myopathic effect of hyperglycaemia, or altered gut hormone secretion.
  - Newer GLP-1 agonist therapies (such as exenatide and liraglutide) used in type 2 diabetes further retard gastric emptying.[1]

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[1] Phillips LK *et al.* (2015). *Nat Rev Endocrinol* **11**: 112–28.

  - Diagnosis best made on gastric scintigraphy performed while euglycaemic. $^{13}CO_2$ breath test or wireless motility capsule are alternatives but less well validated.
  - Management centres on small frequent meals, tight blood sugar control, avoidance of drugs that prolong gastric emptying (calcium channel blockers, opioids, and anticholinergics) and → PROKINETICS such as domperidone (erythromycin less suitable as tachyphylaxis with loss of efficacy after 4wk). Jejunostomy feeding tubes occasionally required. External electrical pacing suggested to provide sustained improvement in gastric emptying in open studies, but not replicated in sham-control trials and complication rate substantial (10% requiring device removal), hence not widely used.
- **Diabetic diarrhoea** occurs with long-standing insulin-dependent diabetes and is associated with ➲ autonomic neuropathy and occasionally faecal incontinence. Differential diagnosis includes ➲ bacterial overgrowth, exocrine ➲ pancreatic insufficiency, associated ➲ coeliac disease, medication side-effect (metformin or acarbose) and ➲ colorectal cancer (meta-analysis of >3 million patients indicates 1.26-fold ↑ relative risk in diabetics).[2] Management is with antidiarrhoeal agents such as loperamide or codeine. → OCTREOTIDE useful in selected patients.

Fatty liver

Abdominal US will often identify 'fatty liver', reflecting accumulation of lipid in hepatocytes. Occurs as part of **metabolic syndrome**, incorporating obesity, hypertension, and diabetes. Proportion of patients with ➲ non-alcoholic fatty liver disease (NAFLD) will have steatohepatitis, which can progress to fibrosis and cirrhosis. Can present with decompensated liver disease. Risk of ➲ hepatocellular carcinoma increased.

Diaphragmatic herniae

Can occur through oesophageal hiatus (see ➲ hiatus hernia), other openings (foramina of Bochdalek at lumbocosatal margins of diaphragm posterolaterally, or Morgagni at sternocostal margins of diaphragm anteriorly) or through post-traumatic defects.

Congenital hernias occur in 0.1–0.5/1,000 live births. In neonates, mostly Bochdalek hernias. Morgagni hernias occur mainly in adults; 80% are on the right side. May contain omentum, stomach, colon, or liver. Repair possible through open, thoracoscopic, or laparoscopic techniques.

Dieulafoy lesion

First described by Georges Dieulafoy, a French surgeon, in 1898. Rare cause of ▲ **acute upper GI bleeding** ▲. Consists of arteriole that protrudes through a 2–5mm mucosal defect, and found in stomach within 6cm of gastro-oesophageal junction in 75–95% of cases (Plate 17). Rarer sites include distal oesophagus, small intestine, colon, and rectum. Diagnosis made on endoscopy. Treatment is endotherapy (e.g. electrocoagulation, adrenaline injection, haemoclipping), which achieves permanent haemostasis in 85%.

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[2] Deng L *et al.* (2012). *Dig Dis Sci* **57**: 1576–85.

Diversion colitis

Inflammation in distal bypassed colon that occurs when faeces is diverted after colostomy or ileostomy. Inflammation seen endoscopically in 90% of patients, and up to 100% histologically. Mild or moderate in 95%, with only 5% severe. Symptoms in <10%, more common in those operated on for IBD, and develop within 1–9mo after diversion.

Pathogenesis

Diversion of faecal stream results in deficiency of ➔ short-chain fatty acids (SCFAs) and other nutrients, and changes in composition of microflora. SCFAs provide 70% of energy used by mucosal cells, and influence mucosal permeability, mucosal blood flow, production of inflammatory cytokines and colonic motility.

Diagnosis and pathological findings

Where there was no preoperative inflammation, diagnosis straightforward. Flexible sigmoidoscopy with biopsy, and exclusion of infection (including ➔ *C. difficile*) will establish diagnosis and severity. Radiology does not help unless fistula or abscess suspected, in which case CT or MRI indicated. Remember to consider radiation or ischaemic colitis in appropriate clinical context.

Differentiating recurrent Crohn's disease from diversion colitis

Can be difficult. Endoscopic features of diversion colitis are non-specific, including erythema, friability, and mucosal granularity. Endoscopic features favouring ➔ Crohn's disease are longitudinal ulcers and strictures, whereas ulcers are usually small in diversion colitis. Absent preoperative rectal involvement can be helpful. Pathological features compared in Table 4.11.

Treatment

Surgical re-anastomosis is the treatment of choice where appropriate. Medical therapy (SCFA enemas and topical 5-ASAs) reserved for those in whom re-anastomosis not appropriate, or possibility of inflammation due to IBD. SCFA enemas (60mM lactate, 30mM propionate, 40mM butyrate) smell awful, and this limits concordance.

Table 4.11 Pathological features of diversion colitis compared to Crohn's disease

Diversion colitis	Crohn's disease
Granulomas can occur but usually mucinous. Transmural changes usually absent	Transmural inflammation, crypt architectural changes (suggests long-standing inflammation), and epithelioid granulomas
Lymphoid hyperplasia with frequent germinal centres very prominent	Lymphoid hyperplasia can occur
Very few macrophages and plasma cells	

Diverticular disease (diverticulosis, diverticulitis, and diverticular bleeding)

A diverticulum (plural: diverticula) is a sac-like protrusion of intestinal wall. Most diverticula of clinical interest occur in colon, but see also ➲ duodenal diverticulum, ➲ Meckel's diverticulum, ➲ jejunal diverticulum, and Zenker's diverticulum (see ➲ pharyngeal pouch).

Colonic diverticula do not contain all bowel wall layers because mucosa and submucosa herniate through the muscle layers at points where vasa recta penetrate circular muscle layer.

Diverticulosis

Prevalence increases with age (5% at 40y; 65% by 85y), and has ↑ markedly in last century. In Western countries, common and usually left-sided: rarer in Far East, more commonly right-sided, and affects younger people. Pathogenesis thought to relate to low dietary fibre.

Diverticulitis

Inflammation of wall and surrounding tissues leads to variable clinical picture, from subclinical inflammation to life-threatening peritonitis. **Simple diverticulitis** is characterized by constant LLQ pain, nausea, or vomiting (in 20–60%), and change of bowel habit. Physical signs include lower abdominal tenderness and abdominal mass (in ~20%). Low-grade fever and leukocytosis common, but ≈50% have normal white cell count. Urinalysis may reveal sterile pyuria secondary to adjacent inflammation. **Complicated diverticulitis** may be accompanied by signs of peritonitis, abscess formation, or fistulation. Faecal discharge from vagina diagnostic of colovaginal fistula, and in the urine of colovesical fistula.

Diagnosis

Erect CXR can help exclude free intraperitoneal air. For further diagnostic information, contrast-enhanced CT scan preferred, and can identify complications of peritonitis, fistula formation, obstruction, and abscess formation. Can also aid therapeutic abscess drainage. In ≈10%, CT unable to distinguish acute diverticulitis from ➲ colon cancer, as both produce focal bowel wall thickening.

Treatment

- Depends on the individual and severity of inflammation. Most patients with simple diverticulitis treated conservatively with broad-spectrum antibiotics with cover directed towards Gram-negative rods and anaerobes (e.g. → CEFUROXIME or → CIPROFLOXACIN + → METRONIDAZOLE).
- Patients with complicated diverticulitis will often need surgery. In the emergency situation, two-stage procedure commonly employed, with resection of diseased colon, oversewing of rectum, and end colostomy (see ▷ 'Hartmann's procedure', p. 190). Colostomy can be closed 3mo later.

Diverticular bleeding

Local trauma to vasa recti within diverticula can lead to arterial bleeding. Most common cause of acute massive colonic blood loss. Although bleeding may stop spontaneously, re-bleeding is common, and often comes from right colon, even though most diverticula left-sided.

Management

After resuscitation, principles are to diagnose and locate source of bleeding, and treat cause (see also ▲ **acute lower GI bleeding** ▲). Colonoscopy reasonable in most patients because blood is cathartic, and visualization of bleeding source may allow endoscopic haemostasis. In patients where colonoscopy is unsuccessful and bleeding is massive, options include angiography or surgery. Diagnostic angiography can be combined with a trial of octreotide infusion to stop bleeding and allow bowel preparation for future intervention, or selective embolization of the bleeding vessel. Important to exclude upper GI sources of bleeding. Surgical options usually involve segmental colectomy.

Double-duct sign

Term used to describe ERCP, MRCP or CT appearance of stricture (and upstream dilatation) of common bile duct and pancreatic duct, usually in patient with biliary obstruction. Often associated with ➲ pancreatic cancer (in head of pancreas, Fig. 4.8). Rarer causes include focal ➲ pancreatitis or ➲ ampullary cancer/stenosis.

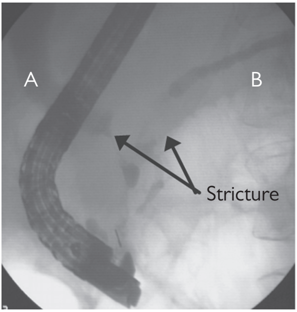

Fig. 4.8 ERCP showing 'double-duct sign'. Stricture of (A) common bile duct and (B) pancreatic duct, in this case associated with cancer in head of pancreas.

Down syndrome and GI tract

Trisomy 21 affects 1:1,000 babies in UK. Characterized by wide range of phenotypic abnormalities including short stature, learning difficulties, wide epicanthic folds, and macroglossia. GI problems can be subdivided into the following:[3,4]

- Embryological (present in 4–10%):
  - Oesophageal atresia/➲ tracheo-oesophageal fistula (0.3–0.8%).
  - ➲ Pyloric stenosis (0.3%).
  - Duodenal/jejunal atresia (1–5%).
  - ➲ Hirschsprung's disease (2%).
  - Imperforate anus (1–4%).
- Motility: feeding problems, constipation, ➲ gastro-oesophageal reflux. In addition, 19–36% have aberrant right subclavian artery, which can cause dysphagia by extrinsic oesophageal compression.
- Immunological:
  - ➲ Coeliac disease: affects >5% (>40-fold ↑ over general population). Early screening appears justified.
  - ➲ Autoimmune hepatitis: probable ↑ frequency.
  - ➲ Hepatitis B (≈25%) and associated autoimmune thyroiditis. Increased HBV infection rate may relate to history of institutional living, but high frequency of chronicity probably due to inherent immune defects.

Drug reaction with eosinophilia and system symptoms (DRESS) syndrome

See: ➲ Drug-induced liver injury, see below.

Drug-induced liver injury

Background

Can occur following use of prescription drugs, over-the-counter medicines, or herbal remedies. Accounts for <5% of cases of jaundice, but one of the commonest causes of ▲ **acute liver failure** ▲. Incidence 10–15/100,000 persons exposed to medications. Risk factors include ♀ sex, old age (may relate to ↓ hepatic blood flow and renal clearance), obesity (e.g. methotrexate-induced hepatic fibrosis), fasting (e.g. paracetamol), multiple drug use (induction of cytochrome P450), alcohol (especially paracetamol, isoniazid, methotrexate), malnutrition, and chronic liver disease (increased risk of anti-TB and HAART-related liver reactions in patients with chronic viral hepatitis). Identifying culprit drug can be difficult, and requires detailed history.

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[3] Weijerman ME & de Winter JP (2010). *Eur J Pediatr* **169**: 1445–52.

[4] Wallace RA (2007). *J Intellect Dis Dev Disabil* **32**: 45–50.

Mechanism of toxicity

Drugs may induce two types of liver injury (see Fig. 4.9):

- Dose-dependent (predictable) hepatotoxic effects: may relate to 'increased dose' (e.g. paracetamol) or 'cumulative dose'.
- Idiosyncratic effects: reaction unpredictable and not dose-related (e.g. hypersensitivity reaction). Onset 5–90d after ingestion, and usually damages hepatocytes, leading to hepatitis (i.e. ↑ AST/ALT). Continued use or re-exposure to drug may be fatal.

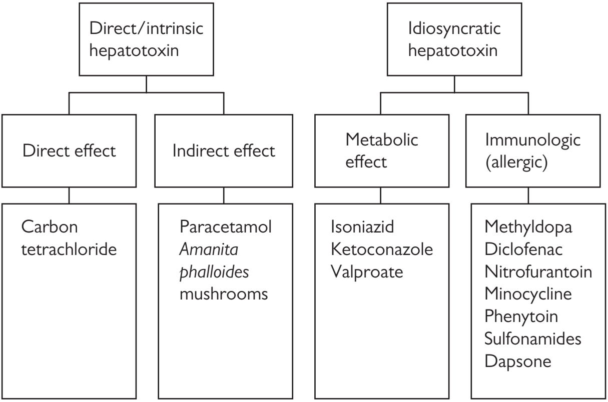
Direct/intrinsic hepatotoxin
Idiosyncratic hepatotoxin
Direct effect
Indirect effect
Metabolic effect
Immunologic (allergic)
Carbon tetrachloride
Paracetamol *Amanita phalloides* mushrooms
Isoniazid Ketoconazole Valproate
Methyldopa Diclofenac Nitrofurantoin Minocycline Phenytoin Sulfonamides Dapsone

Fig. 4.9 Mechanisms of drug-induced liver injury, and examples.

Site of injury

Clues to causative agent may be gained by morphological pattern of liver injury (Table 4.12). Hepatocellular injury may manifest as steatosis, hepatic necrosis, or acute/chronic hepatitis.

Clinical features

- None pathognomonic.
- Fever, rash, and lymphadenopathy may be present in allergic idiosyncratic reactions, and jaundice may be preceded by prodrome of nausea, vomiting, and anorexia (as with viral hepatitis).
- Cholestatic patterns of injury may mimic biliary obstruction (i.e. pruritus and jaundice).
- Can lead to DRESS syndrome (drug rash, eosinophilia, and systemic symptoms). Fever, lymphadenopathy, and multiorgan involvement common; eosinophilia may be absent. May occur some time after drug initiation.

Table 4.12 Common causes of drug-induced liver injury (DILI)

Injury	Common examples	Comments
Hepatocellular	Paracetamol	Hepatic necrosis
	Methotrexate, tetracycline, valproate, herbal remedies, HAART, amiodarone	Steatosis
	Isoniazid, sulfonamides, disulfiram, aspirin, ketoconazole, terbinafine, minocycline	Acute or chronic hepatitis
	Infliximab, diclofenac, indometacin, pegylated interferon, nitrofurantoin, minocycline	➔ Autoimmune hepatitis
Cholestasis	Co-amoxiclav, flucloxacillin, erythromycin, amitriptyline, phenytoin, chlorpromazine, co-trimoxazole	Cholestatic hepatitis (hepatocanalicular)
	Anabolic steroids, oestrogens	Canalicular
Granulomas	Diltiazem, allopurinol, hydralazine, carbamazepine, quinidine, quinine	Varying degrees of cholestasis/hepatitis
Fibrosis	Methotrexate, ethanol	
Vascular	Azathioprine, busulfan, cyclophosphamide	➔ Sinusoidal obstruction syndrome
	Oral contraceptive pill	➔ Budd–Chiari syndrome
	Azathioprine, bush tea, chemotherapy	➔ Nodular regenerative hyperplasia
	Vitamin A, methotrexate, didanosine	Non-cirrhotic portal hypertension

Specific drug groups

Paracetamol

See ➔ paracetamol overdose.

Aspirin and NSAIDs

See ➔ NSAIDs and the GI tract.

Statins

↑ AST/ALT in 3%, generally transient. Very few documented cases of severe liver injury, particularly given widespread use, and no evidence less safe in chronic liver disease. ▲ **Acute liver failure** ▲ idiosyncratic, occurring in $1/10^6$ patient-years (~background rate of idiopathic liver failure). Several guidelines advocate LFT monitoring 12wk after statin initiation, and annually thereafter, although no evidence this strategy prevents significant DILI, and may lead to premature discontinuation of beneficial cardiac drugs.

Anticonvulsants

Hepatotoxicity often due to toxic metabolites. Cause 6–8% of DILI.

- *Phenytoin* Can cause acute or chronic hepatotoxicity. No correlation between serum concentration and DILI, or between liver and central nervous system toxicity. DILI usually reverses following drug cessation, although overall mortality 13%. Patterns of injury include: ↑ ALP/γGT; hypersensitivity with fever, rash, and eosinophilia; acute hepatitis; and chronic liver injury (typically when drug not discontinued in face of abnormal LFTs).
- *Carbamazepine* As with phenytoin, DILI does not correlate with serum drug concentration. At least 10% of patients develop asymptomatic ↑ ALT/AST/ALP, and up to 60% ↑ γGT. These are generally not sufficiently high to recommend drug cessation, although severe reactions may occur (especially in children). Patterns of injury include cholestasis; hepatic necrosis; granulomatous hepatitis; hypersensitivity; and vanishing bile duct syndrome.
- *Sodium valproate* Reversible ↑ ALT/AST occurs in 10–40% during first few months of treatment, and often normalizes despite continuation of therapy. Clinically significant DILI in 1/15,000 (more frequent in children). Three main subtypes recognized:
  - **Toxic hepatitis** Submassive/zonal hepatocyte necrosis in 1/37,000, mostly within 3mo of starting therapy. Associated with carnitine depletion (essential co-factor in mitochondrial fatty acid β-oxidation). Outcomes better with levocarnitine supplementation.
  - **Hyperammonaemia** can develop in up to 50% as valproate disrupts urea cycle. Rarely clinically significant.
  - **Reye-like syndrome** can occur, with microvesicular steatosis.
- *Other anticonvulsants* Isolated reports of acute hepatitis or fulminant hepatic failure with lamotrigine, levetiracetam, topiramate, oxcarbazepine, and phenobarbital. Clinically significant hepatotoxicity not reported with tiagabine, benzodiazepines, or ethosuximide.

Antidepressants

Significant DILI rare. Abnormal LFTs in 0.5% patients on long-term therapy with *selective serotonin reuptake inhibitors* (SSRIs); cholestasis reported particularly with sertraline. *Tricyclic antidepressants* principally cause cholestatic injury, but rarely associated with hepatocellular damage or vanishing bile duct syndrome. Acute hepatitis is feature of *monoamine oxidase inhibitors* (incidence 1%), particularly iproniazid (now withdrawn in UK). The *serotonin-noradrenaline reuptake inhibitors* venlafaxine and nefazodone have been associated with severe hepatocellular injury and fulminant liver failure.

Amiodarone

Asymptomatic ↑ occur in up to 25% on long-term therapy, but symptomatic DILI in <1%. Both acute fulminant hepatitis and chronic hepatitis with cirrhosis can develop.

Antituberculosis drugs

Several antimicrobials employed in treatment of TB have potential to cause DILI, and ≈10% of patients receiving anti-TB treatment will develop deranged serum aminotransferases (of whom 10% at risk of severe hepatic necrosis). Monthly LFT monitoring required in those with abnormal baseline results, those with liver disease, in pregnancy and for 3mo post-partum, and those receiving pyrazinamide. As many drugs used in combination therapy could be responsible for DILI, should this arise it is usually appropriate to temporarily stop all agents and rapidly exclude other causes of liver disease. To restart, it is generally recommended to commence with rifampicin, followed by ethambutol. If these are tolerated for at least 7d, isoniazid can be reintroduced. If DILI recurs, remove the last drug added. Avoid pyrazinamide if hepatotoxicity prolonged or severe. Some experts provide 2nd line agents to avoid complete treatment cessation (e.g. an aminoglycoside or moxifloxacin).

- *Rifampicin* Can cause dose-dependent interference with Bn uptake, resulting in subclinical unconjugated hyperbilirubinaemia without hepatocellular damage. Also potentiates hepatotoxicity of other drugs. ALT ↑ in 20%, and >2x ULN in 2.5%. Hepatocellular injury rare, and often hypersensitivity reaction. Conjugated hyperbilirubinaemia can result from inhibition of bile exporters.
- *Isoniazid* Predominantly cleared via acetylation by *N*-acetyltransferase-2 to toxic monoacetyl hydrazine, then to non-toxic diacetyl hydrazine. Genetic polymorphisms correlate with fast, slow, and intermediate acetylator enzyme action. Most cases of presumed isoniazid hepatotoxicity in fact associated with pyrazinamide use. Up to 20% of patients get ↑ ALT/AST, but usually modest and transient with only 0.1–2% developing clinical hepatitis. Risk lower in Afro-Caribbean individuals.
- *Pyrazinamide* Frequently used in combination therapy, and many believe responsible for much of DILI attributed to isoniazid. Exhibits both dose-dependent and idiosyncratic hepatotoxicity (including hypersensitivity with eosinophilia, and granulomatous hepatitis). Not usually restarted if thought to have caused DILI.
- *Other anti-TB drugs* Hepatotoxicity uncommon with *rifabutin* at usual doses but may be seen in high doses combination therapy with macrolides used to treat disseminated atypical mycobacterial infection. Single report of cholestatic jaundice with *ethambutol*, but not definitively attributable to the drug. Fluoroquinolones (e.g. ciprofloxacin and moxifloxacin) partly metabolized by liver; reversible transaminase elevation occurs in 2–3%, and severe hepatocellular injury and cholestasis in <1%.

Co-amoxiclav

Frequent cause of DILI, principally due to clavulanic acid component. Symptomatic hepatitis in 3–17/100,000. Jaundice most commonly cholestatic, developing 1–4wk (but reported up to 8wk) after drug cessation. Pathologically associated with ductopaenia (vanishing bile duct syndrome). Typically follows benign course and resolves within 2mo. Hepatocellular injury rare but can present in 1st wk. More frequent in younger patients, compared to cholestatic injury that typically affects older adults. Usually mild with complete recovery, but outcome can be severe or protracted (3% die or require liver transplant, 7% sustain persistent liver injury).

Minocycline

Tetracycline antibiotic, widely used in young patients for treatment of acne vulgaris. Associated with 3 patterns of DILI: dose-related direct hepatotoxicity with severe steatosis (mostly reported with IV administration); allergic idiosyncratic reactions (may cause DRESS); and autoimmune hepatitis (often associated with arthralgia/arthritis, fever, and rash; mean onset 15mo post-exposure and 90% strongly positive for ANA). Treatment involves drug discontinuation ± steroids for non-resolving allergic/autoimmune subtypes.

Oral contraceptive pill

See ➔ oral contraceptive pill.

Khat

Chewing khat leaves (*Catha edulis*) common in East Africa and Arabian Peninsula. Leaves contain cathine and cathinone, which have amphetamine-like effects. Can cause ▲ **acute liver failure** ▲. Use should be suspected when patients from communities where consumption is prevalent present with unexplained liver injury.

Herbal remedies

Use increasingly common, and agents can cause most patterns of liver injury.[5] Accurate history required, although information concerning ingestion may be withheld. Patient education important, including the notion that 'natural' ≠ 'safe'. Compounds may consist of mixtures that are often impure, and botanicals may be misidentified or contaminated (e.g. with pesticides). In absence of history, their use should be suspected with unusual patterns of liver injury, including zonal necrosis, steatosis, bile duct injury, and ➔ sinusoidal obstruction syndrome.

Diagnosis/investigation

- Usually no specific diagnostic tests (except in ➔ paracetamol overdose), so relies on clinical suspicion, careful drug history (including all prescribed, complementary, and recreational drugs), consideration of temporal relationships between drug ingestion and liver disease, and exclusion of other disorders.
- 'Liver screen' of blood tests help define pattern and severity of injury, and exclude other causes (see ► Approaches to recent-onset jaundice and ► Approach to well patients with abnormal liver tests).
- Serum ALT >1,000IU/L strongly suggests drug injury, acute viral hepatitis, or hepatic ischaemia.
- Peripheral eosinophilia may point towards allergic drug reaction.
- Liver US excludes biliary obstruction in patient with cholestasis.
- Liver biopsy findings rarely specific for a drug reaction (although eosinophils and granulomas may be suggestive).

Avoid diagnostic re-challenge with suspected drug in almost all cases (risk of even more severe reaction) unless drug toxicity highly questionable or no alternative to suspected drug for a serious condition.

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[5] Seeff LB *et al.* (2015). *Gastroenterology* **148**: 517–27.s

Management

- Stopping causative drug is the fundamental intervention (failure to do so is associated with high mortality). In patients on a combination of drugs, the one started most recently may be likeliest culprit. Nevertheless, stopping all drugs is the wisest manoeuvre, if clinically possible. If the patient improves, drugs least likely to be responsible may be carefully sequentially reintroduced.
- → CORTICOSTEROIDS used for severe allergic-type reactions, and → URSODEOXYCHOLIC ACID (UDCA) for cholestatic reactions, but no clear trial evidence of benefit.
- Patients with evidence of liver failure (e.g. INR >1.5, or ▲ **hepatic encephalopathy** ▲) require transfer to ➲ liver transplantation centre (see also ▲ **acute liver failure** ▲).

Drug-induced oesophagitis

- Patients with pill-induced oesophageal injury usually present with sudden-onset chest pain, dysphagia, and odynophagia. Damage made more likely by a number of factors:
  - ↓ Salivary flow (ageing, sicca symptoms, anticholinergic drugs).
  - Disordered oesophageal motility.
  - Disordered local motility (enlarged left atrium).
  - Medication formulation (capsule, large tablets).
  - Medications affecting tone of lower oesophageal sphincter (benzodiazepines, α-blockers, theophyllines, opioids, calcium channel blockers, nitrates).
  - Ingestion when lying flat (night-time).
- Many drugs reported to cause oesophageal injury (Box 4.18). 90% of cases due to NSAIDs, antibiotics (especially tetracyclines), antivirals, potassium chloride, iron, quinidine, and bisphosphonates.
- Patients with strictures, ➲ oesophageal tumour, ➲ achalasia, or ➲ systemic sclerosis should take pills upright with plenty of water.

Chemotherapy oesophagitis

Doxorubicin, fluorouracil, → METHOTREXATE, and vincristine can all cause oropharyngeal mucositis and consequent dysphagia. Oesophageal damage unusual in absence of oral changes. Chemotherapy potentiates radiation damage to oesophagus.

Box 4.18 Causes of drug-induced oesophagitis

- **NSAIDs** including aspirin.
- **Antibiotics**: tetracyclines, clindamycin, penicillins.
- **Antivirals**: AZT, ddC, foscarnet.
- **Iron** and **potassium** formulations.
- **Cardiovascular medications:** quinidine, nifedipine, verapamil, captopril.
- **Other common drugs:** bisphosphonates, phenytoin.

Dubin–Johnson syndrome

Rare autosomal recessive cause of conjugated hyperbilirubinaemia (see ► Approach to recent-onset jaundice and ➲ bilirubin metabolism). Impaired canalicular excretion of conjugated bilirubin leads to mild jaundice (Bn <120μmol/L, 50% conjugated) with normal liver function. Black pigment in hepatocytes on biopsy (differentiates from ➲ Rotor syndrome). No specific treatment. Prognosis good.

Dukes staging system

Developed by Cuthbert Esquire Dukes, 1932. A classification of ➲ colon cancer invasion still in use because the relation of advancing stage to cancer mortality has been repeatedly demonstrated.

- **Stage A** tumours mucosal (may invade into submucosa but do not reach muscularis propria). 5y survival 95–100%.
- **Stage B1** tumours invade muscularis propria, and **B2** lesions completely penetrate smooth muscle layer to serosa but without lymph node involvement. 5y survival 80–85%.
- **Stage C** lesions defined by regional lymph node involvement. Further divided into primary tumours limited to bowel wall (**C1**) and those that penetrate bowel wall (**C2**). 5y survival 50–70%.
- **Stage D** lesions include all with metastases. 5y survival 5–15%.

The American Joint Commission on Cancer devised the ➲ TNM classification, which has largely replaced Dukes staging system for randomizing patients into clinical trials. Comparison of Dukes with TNM yields the following:

- Dukes A = T1/2, N0, M0.
- Dukes B = T3/4, N0, M0.
- Dukes C = T1–4, N1 or N2, M0.
- Dukes D = M1.

Dumping syndrome

Aetiology and pathogenesis

One of a number of post-gastrectomy syndromes (see also ▷ p. 184), resulting from disturbed gastric storage and pyloric emptying. Allows stomach contents to be emptied too rapidly, filling small intestine with undigested food inadequately prepared for efficient absorption. Incidence relates to extent of gastric surgery and may affect 20–25% of patients. Syndrome much less common now because of declining number of operations for ➲ peptic ulcer disease (following discovery of ➲ *H. pylori* and advent of → PROTON PUMP INHIBITOR therapy), as well as lower incidence of gastric emptying complications with newer operations such as proximal gastric vagotomy.

Clinical features

Symptoms often divided into ‘early’ or ‘late’, depending on relation to meals. Most patients experience combination of the two:

- **Early dumping** can occur during meal or up to 60min after eating. Thought to result from accelerated emptying of hyperosmolar gastric contents into small bowel leading to fluid shifts from intravascular compartment into bowel lumen triggering **vasomotor symptoms**: tachycardia, vasodilatation, sweating, and light-headedness as well as **distension**, **crampy pain**, and **diarrhoea**. Post-prandial release of gut hormones (enteroglucagon, peptide YY, pancreatic polypeptide, VIP, neurotensin) ↑ in patients with dumping, some of which may play a part in the pathogenesis.
- **Late dumping** occurs 1–3h after meal. Rapid delivery of meal to small intestine leads to rapid absorption of glucose and hyperinsulinaemic response, causing hypoglycaemia.

Diagnosis

- Primarily based on development of symptoms in patient with history of gastric surgery.
- Gastric emptying scintigraphy may demonstrate rapid emptying.
- Resultant hypoglycaemia can be confirmed by extended glucose tolerance test.

Management

Postoperative dumping tends to improve with time. Management primarily involves dietary modification, with medications reserved for refractory or severe cases.

- Dietary modification should include eating smaller, more frequent meals with high protein, fat, or soluble fibre content. Complex carbohydrates should be eaten in preference to simple sugars.
- Fluid consumption should be limited during meals and nutrient-rich drinks (e.g. nutritional supplements) avoided.
- If pharmacological adjuncts required, some evidence to support use of → OCTREOTIDE to delay gastric emptying. Acarbose useful in late dumping syndrome as interferes with carbohydrate absorption.

Duodenal diverticulum

- Peri-ampullary diverticula common finding at ▹ ERCP. Debated whether associated with common bile duct (CBD) stones and biliary obstruction. Presence may make CBD cannulation difficult (and occasionally impossible), and particular care during biliary sphincterotomy is essential to avoid retroperitoneal perforation. Food debris in diverticulum may be confused on US or MRCP as an intraductal filling defect.
- Large diverticula may occur elsewhere in small bowel (see ➔ jejunal diverticulum), where may cause abdominal discomfort, diarrhoea, and ➔ bacterial overgrowth. Many diagnosed incidentally on imaging.

Duodenal ulcer (see Plate 19)

Pathogenesis, epidemiology, treatment, and complications discussed in ➲ peptic ulceration.

Management recommendations

Do not take biopsies routinely at endoscopy because malignancy is extremely rare. Take CLO test or alternative to establish ➲ *Helicobacter pylori* status and treat if positive. Continue antisecretory treatment with → PROTON PUMP INHIBITORS for at least 4wk. Although PPIs are the most common drugs used, no clear evidence of their superiority over other drugs for uncomplicated DU in patients not taking NSAIDs.

If symptoms resolve and compliance with treatment is good, routine follow-up endoscopy and confirmation of *H. pylori* eradication are not necessary. However, follow-up endoscopy is suggested for complicated ulcers that have bled or perforated. Studies on maintenance therapy for such ulcers are limited, and this issue remains disputed. Consider maintenance if recurrence would be high risk (elderly, severe comorbidity).

Consider hypersecretory states such as ➲ Zollinger Ellison syndrome, ➲ multiple endocrine neoplasia, and antral G cell hyperplasia as rare causes of duodenal ulcers.

Dye spraying

See: ▹ 'Chromoendoscopy', p. 169.

Dysentery

A clinical term: bloody mucoid diarrhoea, tenesmus, fever, cramps, and polymorphs in faeces. Implies invasive pathogen affecting large bowel, commonly ➲ *Shigella*, enteroinvasive or enterohaemorrhagic ➲ *E. coli*, or ➲ amoebiasis (note: does not give leucocytes in the stool). See ► Approach to acute diarrhoea.

Dysplasia

A term that induces frustration and uncertainty into the hearts of gastroenterologists, particularly when they want a straight answer from the pathologist: 'Is it cancer or not?'

- Dysplasia refers to **cellular and architectural changes that are associated with malignancy** (pre-malignant/adjacent to malignancy) but that, by definition, are not invasive. Differentiate from metaplasia, which refers to conversion of one type of differentiated tissue into another specialist type (e.g. intestinal metaplasia in stomach related to *H. pylori*).
  - **Cellular changes** in dysplasia include an increase in cell nuclei size (↑ nuclear:cytoplasmic ratio), loss of nuclear polarity, and loss of cellular differentiation (e.g. mucin production).
  - **Architectural changes** include loss of normal glandular spacing without intervening stroma.
- In practical terms, high-grade dysplasia on mucosal biopsy suggests significant risk of invasive malignancy developing, or being present at other sites (in view of tiny area of tissue sampled). Unless confident that all affected areas are removed (e.g. excised polyp), high-grade dysplasia requires consideration of radical intervention (e.g. colectomy in ulcerative colitis, oesophagectomy in ➔ Barrett's oesophagus).
- Vienna classification of GI epithelial neoplasia (Table 4.13) aims to standardize reporting of dysplasia/neoplasia.

Table 4.13 Vienna classification of GI epithelial neoplasia

Category	Histological assessment
1	Negative for neoplasia/dysplasia
2	Indefinite for neoplasia/dysplasia
3	Non-invasive low-grade neoplasia (low-grade adenoma/dysplasia)
4	Non-invasive high-grade neoplasia
4.1	High-grade adenoma/dysplasia
4.2	Non-invasive carcinoma (carcinoma *in situ*)
4.3	Suspicion of invasive carcinoma
5	Invasive neoplasia
5.1	Intramucosal carcinoma
5.2	Submucosal carcinoma or beyond

E

Eating disorders: see ► Approach to eating disorders, ➔ Anorexia nervosa, ➔ Bulimia, *332*

Ectopic mucosa *332*

Ehlers–Danlos syndrome *332*

Elemental diets *333*

Encephalopathy: see ▲ **Hepatic encephalopathy** ▲ *334*

Endocarditis: see ⊳ 'Antibiotic prophylaxis' (p. 198) *334*

Endometriosis affecting the GI tract *334*

Enteral tube feeding *334*

Eosinophilia and the GI tract *336*

Eosinophilic gastroenteritis on *336*

Eosinophilic oesophagitis *337*

Erythema nodosum (EN) *339*

Escherichia coli *339*

Exclusion diets *340*

Extracorporeal shock-wave lithotripsy (ESWL): see ➔ Lithotripsy *340*

Eating disorders

See: ▶ Approach to eating disorders, ➲ Anorexia nervosa, ➲ Bulimia.

Ectopic mucosa

Refers to mucosal tissue at sites distant from normal location. Still debated as to whether these are embryological remnants or acquired. Mostly benign and asymptomatic, but can rarely be functional (i.e. hormone-secreting) or undergo malignant transformation. Common examples:

- Meckel's diverticula (often harbour gastric mucosa).
- Pancreatic rests. Islands of acinar tissue, lacking anatomic and vascular continuity with main pancreas. Found in 1–14% autopsies. Most common in stomach and duodenum, where appear as yellow submucosal nodules. Usually asymptomatic, requiring no treatment.
- Gastric heterotopia. Mostly duodenal, but described in all parts of gastrointestinal (GI) tract. Sessile/polypoid lesions. Usually asymptomatic finding on endoscopy, but histology necessary to exclude other causes.

Ehlers–Danlos syndrome (see Plate 48)

Pathogenesis

Described by Edvard Ehlers (Danish dermatologist) in 1901 and Henri-Alexandre Danlos (French physician) in 1908. Diverse group of inherited connective tissue disorders, resulting in decreased tensile strength and integrity of skin, joints, blood vessels, and tissues of GI tract. Historically classified as types I–X, but in 1997 system revised to 6 major variants, named descriptively. Most common is hypermobility subtype (previously type III; prevalence up to 1/5,000). Classical subtype (previously types I & II) is rarer (1/20,000); shares features of type III but with more severe cutaneous involvement. Vascular subtype (previously type IV) is the most severe.

Clinical features

Hypermobility and classical subtypes

GI problems are very common (>50% patients), impact on quality of life, but do not typically cause serious complications (with exception of vascular subtype, see next). Most frequent are ➲ irritable bowel syndrome-like symptoms and heartburn. Dysautonomia, ➲ hiatus hernia, and diverticulosis frequently demonstrable. Abdominal wall hernias present in 20%, hepatic ➲ haemangiomas are relatively common, and rectal prolapse is seen in 10%.[1] Intra-abdominal organ ptosis described in case series but of uncertain relevance.

Extra-gastrointestinal features include hypermobile joints (hyperextension of digits, wrists, knees, elbows), arthralgia, recurrent joint dislocations/subluxations, soft tissue inflammation (epicondylitis, tenosynovitis, bursitis), Marfanoid habitus, hyperextensible thin skin with papyraceous scarring or striae, hernias, and varicose veins.

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[1] Nelson AD *et al*. (2015). *Neurogastroenterol Motil* **27**: 1657–66.

Vascular subtype

More severe. Prevalence 1/100,000, and only type with ↑ mortality (median life expectancy 50y). Caused by mutations in type III collagen. Characteristic appearance: small chin, thin nose, lobeless ears, translucent skin, and easy bruising. GI symptoms typically similar to hypermobility subtype but, in addition, can present with spontaneous rupture of medium-sized thoraco-abdominal arteries or bowel—i.e. as GI bleed. Mega-oesophagus; spontaneous intramural haematoma; and hepatic, splenic, and gallbladder rupture also reported. Surgery challenging in these patients as tissues do not hold sutures well, often get substantial intraoperative bleeding, and almost invariably develop adhesions and hernias postoperatively, therefore tend to avoid unless life-threatening situation.

Diagnosis

Clinical for hypermobility variant (no common genes identified to date); refer to physician with interest in disorder (see also: Brighton criteria 🖱 http://www.ehlers-danlos.org/about-eds/getting-a-diagnosis/brighton-score/). Remainder usually diagnosed based on clinical suspicion, followed by specific testing to confirm mutated collagen gene.

Management

Mostly symptom-driven. Avoid constipation (use stool softeners if necessary). Exercise caution if performing colonoscopy (particularly in vascular subtype), as ↑ risk of perforation. If needed, can consider computed tomography (CT) colonography as alternative, but do not neglect potential lifetime diagnostic radiation exposure in polysymptomatic patients with frequent medical complications.

Elemental diets

- Originally designed for the United States (US) manned space programme, but when used while preparing some patients for surgery, coincident benefit noted in ➔ Crohn's disease. Possible mechanisms include effects on microbiome or mucosal permeability, with additional benefits from improved nutritional state. Use is attractive in children (where → CORTICOSTEROIDS affect growth) and pregnancy (↓ drug usage).
- Several studies showed equivalence with steroids in achieving short-term remission in Crohn's disease (particularly in children). Patients with small bowel disease may benefit more, and may ↓ recurrence and need for biologic therapy following surgery. Those with perianal disease, or who relapse quickly, should avoid. Efficacy higher in children than adults.
- Dietary composition varies. Elemental diets include polymeric feeds using whole protein and complex carbohydrate; peptide-based diets (containing di- and tri-peptides, thought better absorbed than amino acids); and true elemental feeds (containing amino acids, glucose, and short-chain triglycerides). Available data suggest little difference. Has been concern that fat content may influence response (i.e. poor response to feeds containing long chain fatty acids and better with medium chain fats), but little evidence to support this. Compliance is an issue: 85% manage sip feeding but 15% require nasogastric (NG) tube.

Encephalopathy

See: ▲ **Hepatic encephalopathy** ▲.

Endocarditis

See: ▹ 'Antibiotic prophylaxis', p. 198.

Endometriosis affecting the GI tract

Endometrial tissue may arise outside uterus, usually without symptoms, in 15% of menstruating women. In those undergoing surgery for endometriosis, 30% have intestinal involvement, usually rectosigmoid. Penetration of endometriomas into bowel rare but can cause partial obstruction, with pain and constipation. GI bleeding unusual: deposits do not usually invade mucosa but are associated with muscular hypertrophy and fibrosis. Malignant degeneration rare but documented.

Diagnosis

Can be difficult; <50% have cyclical symptoms associated with menses, but nearly all women with intestinal involvement have associated features of pelvic endometriosis.

Investigation

- Transvaginal US 1st line.
- CT and MRI usually non-specific because of small size of deposits.
- Endorectal US may identify lesions, but cannot differentiate from other pathologies.
- Rectal biopsy often normal unless associated bleeding. Very rarely, mucosal invasion can simulate adenomatous polyps.
- Laparoscopy can be diagnostic, and allows tissue sampling.

Treatment

Combined oestrogen-progesterone, or progesterone only, contraceptives 1st line. If these fail, surgical resection usually recommended (3–10% have major complications). If ovarian function is preserved, symptom recurrence is common.

Enteral tube feeding

In patients who need supplemental feeding, enteral tube feeding has many advantages over ➲ parenteral nutrition (Box 4.19). See also ► Approach to nutritional support. Feeding regimens use defined **liquid formula feeds**. Although pure sources of protein, carbohydrate, and lipid are available ('feeding modules'), these are rarely used in our experience.

Box 4.19 Why is enteral feeding preferable to parenteral nutrition (PN)?

- No need for central venous feeding line, resulting in fewer line-related complications (such as line sepsis and thrombosis).
- Enteral feeding can supply gut-preferred fuels such as glutamine and short-chain fatty acids, often absent from PN preparations.
- Enteral feeding can prevent mucosal atrophy, preserves mucosal and pancreatic enzyme function, and maintains GI IgA secretion.
- Enteral feeding may reduce risk of cholelithiasis, by stimulating gallbladder motility (gallstone formation is a common problem in patients on PN, especially if little or no oral intake).
- Enteral feeding requires less frequent monitoring of electrolytes and volume status ∴ less expensive to provide.

Choice of enteral feed is influenced by patient nutritional requirements; any abnormality of gastrointestinal absorption, motility, or diarrhoeal losses; and presence of any other system abnormality (such as renal or liver failure). Most commercial feeds contain 1kcal/ml, with higher energy versions containing 1.5kcal/ml. They are generally available in fibre-free and fibre-enriched forms.[1]

Polymeric feeds

Contain nitrogen as whole protein. Carbohydrate source partially hydrolysed starch, and fat contains long chain triglycerides. Most polymeric feeds are lactose-free, containing casein or soy as protein source. Fibre content variable, and not present in most lactose-free formulas.

Predigested feeds

Contain nitrogen either as short peptides (oligomeric feeds) or as free amino acids in case of ➔ elemental diets (monomeric feeds). Carbohydrate provides much of the energy source, with content variable in both quantity and proportion provided as long and medium chain triglycerides. The aim of 'predigested diets' is to improve nutrient absorption in the presence of significant malabsorption. Importance considered greater in maldigestive (e.g. pancreatic disease) rather than malabsorptive states. Note that in patients with short gut and no colon, their high osmolality can cause excess movement of water into gut and hence higher stomal losses.

Guideline

Guideline (2003) for enteral feeding in adult hospital patients. 🖱 http://gut.bmj.com/content/52/suppl_7/vii1.long.

Eosinophilia and the GI tract

Eosinophils are bone marrow-derived leukocytes, typically present at $<0.4 \times 10^9$ cells/L in circulating blood. Elucidating cause of eosinophilia involves careful history (including travel, geographic exposures, and medication use), thorough examination (close attention to skin, masses, and adenopathy), then specific tests guided by possible causes (Box 4.20). Causes of hypereosinophilia + GI symptoms include:[2]

- **Infection** Typically helminths (commonest cause worldwide). Tend to elicit most marked eosinophilic responses when breach mucosal barriers, particularly during migration. Culprits include hookworm, ascaris, and trichuris (see ➲ roundworms); ➲ strongyloides, ➲ clonorchis, filariasis, ➲ schistosomiasis, and *Fasciola* (may present with right upper quadrant (RUQ) pain, fever, and hepatomegaly). Infections with protozoa (e.g. ➲ giardiasis) rarely cause eosinophilia.
- **Atopy/allergy** Asthma and allergic rhinitis are common, and may coexist with GI disease.
- **Drugs** Antibiotics (especially penicillins, cephalosporins and sulfonamides), quinine, non-steroidal anti-inflammatories (NSAIDs), carbamazepine. See also ➲ drug-induced liver injury and ➲ drug reaction with eosinophilia and systemic symptoms (DRESS).
- **Haematological** Leukaemic malignancies, mastocytosis.
- **Immunological/rheumatological** ➲ Vasculitis (e.g. Churg–Strauss syndrome), ➲ dermatomyositis, ➲ systemic sclerosis, ➲ graft-versus-host disease.
- **Endocrine** Addison's disease.
- **Organ-restricted involvement** ➲ Eosinophilic gastroenteritis, ➲ eosinophilic oesophagitis.

Box 4.20 Basic 'package' of investigations for returning travellers with eosinophilia[3]

All areas:

- Stool microscopy for ova, cysts, and parasites.
- ➲ Strongyloides serology.

+ *if travel to Africa*:

- Terminal urine microscopy for ➲ schistosomiasis.
- Schistosoma serology.
- Filarial serology (optional as 1st line investigation).

Eosinophilic gastroenteritis on

Rare disease, usually presenting at age 30–50y. Diagnostic criteria:

- Presence of GI symptoms (usually abdominal pain).
- High eosinophilic infiltrate (usually 15–20/high power field) in 1 or more areas of GI tract on biopsy.
- Absence of organ involvement outside GI tract.
- Absence of other causes of ➲ eosinophilia.

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2 Nutman TB (2007). *Immunol Allergy Clin North Am* **27**: 529–49.

3 Checkley AM *et al*. (2010). *J Infect* **60**: 1–20.

Pathogenesis

Poorly understood but involves damage to gut wall through eotaxin and Th2 cytokine-mediated eosinophil degranulation. Trigger unknown but may involve type 1 hypersensitivity.

Clinical features

Stomach and small intestine most commonly affected but any part of GI tract can be involved. Most commonly affects mucosa and submucosa, causing colicky pain, nausea, vomiting, diarrhoea, and weight loss. If muscle layer mainly affected, presentation can be with pyloric or upper GI obstruction. Very rarely serosal disease can cause eosinophilic ascites. History of atopy or food allergy often identified.

Investigation

50% have peripheral blood eosinophilia. Serum iron and albumin may be low. IgE may be raised, especially in children. Stool studies and serology necessary to exclude parasitic infestation. Histological samples from affected areas needed for diagnosis.

Treatment

- If no muscle/serosal involvement, dietary manipulation reasonable, especially if history suggestive of food intolerance. Children often respond well—milk protein is most frequently implicated allergen.
- If history of travel or residence in high-risk areas, trial of antiparasitic therapy (e.g. mebendazole 100mg bd for 3d) reasonable.
- → CORTICOSTEROIDS (usually prednisolone or budesonide) used in patients who fail to respond to aforementioned measures, or with obstructive symptoms or eosinophilic ascites. 90% respond to oral prednisolone at dose of 20–40mg/d, tapered over several weeks; symptomatic improvement usually seen within days to weeks. 30–50% will relapse on discontinuation. Use of 2nd-line immunosuppressives in patients who are steroid-dependent has not been examined systematically.
- → CROMOGLICATE (200mg tds-qds) often tried. Stabilizes mast cells and can ↓ antigen absorption by small intestine.
- Montelukast. Use for several months at dose of 10–40mg/d improves symptoms and peripheral eosinophilia.
- Preliminary studies suggest utility of IL-5, eotaxin-1, or CCR3 blockade, although definitive trials required.

Eosinophilic oesophagitis (see Plate 12)

First described in 1978, eosinophilic oesophagitis (EoE) now increasingly recognized.[4] Chronic relapsing-remitting, T cell-mediated allergic immune response to food allergens. Other causes of oesophageal eosinophilia rare (oesophageal helminth infection, ➲ lymphoma, ➲ herpes, ➲ candida, ➲ drug-induced oesophagitis, ➲ Crohn's disease, ➲ vasculitis). Relationship with ➲ gastro-oesophageal reflux (GORD) complex: oesophagitis can lead to eosinophilia (albeit in reduced concentration and primarily in distal oesophagus), GORD can exacerbate symptoms of underlying EoE, and subset of EoE seems to be → PROTON PUMP INHIBITOR responsive.

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[4] Glenn T *et al*. (2015). *N Engl J Med* **373**: 1640–8.

Diagnostic criteria

Evolving. Current expert opinion suggests:

- Clinical symptoms of oesophageal dysfunction: solid food dysphagia, non-cardiac chest pain, food impaction, and (in some cases) refractory reflux-like symptoms with no objective evidence of GORD.
- Exclusion of GORD.
- Exclusion of other conditions causing oesophageal eosinophilia.
- Histological mucosal eosinophil count ≥15/HPF. At least 5 biopsies should be taken from proximal, mid, and distal oesophagus.

Practice point: Assessment of dysphagia

All patients with dysphagia of unclear aetiology, food bolus obstruction, strictures/➔ Schatzki ring, non-cardiac chest pain, or refractory reflux-like symptoms undergoing endoscopy should always have biopsies taken as part of routine protocol.

Endoscopic signs

Endoscopy normal in up to one-third of patients. Pathognomonic mucosal changes include:

- Early: oedema, white spots/exudates, furrows, corrugated rings.
- Late: strictures, narrow calibre oesophagus (features of fibrosis and remodelling).[5]
- EoE is most common cause of spontaneous oesophageal perforation.

Therapeutic options

- Dietary therapy. 6-food elimination diet (milk, egg, wheat, soy, peanuts, and seafood), elemental, or targeted elimination based on allergy testing (more common in children).
- → PROTON PUMP INHIBITOR. To treat underlying reflux disease if culprit or contributory. Also emerging evidence of potential anti-inflammatory effects independent of those on acid secretion.[6]
- Topical steroid (e.g. fluticasone propionate, budesonide) most effective therapy in adults. Formulation should be swallowed, not inhaled, 1–2×/d (depending on severity), with no eating or drinking for 30min afterwards. Therapy should then persist at lowest effective dose, with option of intermittent escalation guided by symptoms.
- Systemic steroids should only be used for acute severe disease, as a bridge to topical steroids.
- Dilatation should be considered in patients with fibrotic narrowing if at risk of dehydration or malnutrition, but steroids should be commenced before, and continued after, therapy. Steroids alone may alleviate non-occlusive strictures and avert need to dilate.

Prognosis

Few longitudinal studies, but in general follows chronic or relapsing course. Children frequently develop strictures if disease uncontrolled.

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[5] Hirano I *et al*. (2013). *Gut* **62**: 489–95.

[6] Cheng E *et al*. (2013). *Gut* **62**: 824–32.

Erythema nodosum (EN)

Red, well-demarcated, bilateral, tender, raised 1–5cm nodules, usually on shins (Plate 44). Causes: infection (*Streptococcus*, ➔ *Campylobacter*, TB, ➔ *Yersinia*, fungi), drugs (sulfonamides, penicillins, ➔ oral contraceptive pill), ➔ sarcoidosis, ➔ Behçet's disease, lymphoma. One-third idiopathic. Occurs in ~2% of inflammatory bowel disease (IBD) patients (➔ Crohn's disease, ➔ ulcerative colitis), and usually parallels disease activity. Histology shows panniculitis. Lesions typically resolve spontaneously in 6wk. NSAIDs may help, as does control of underlying IBD activity.

Escherichia coli

Major component of normal intestinal flora. Six pathogenic subtypes:

- **Enteropathogenic *E. coli* (EPEC)** Causes watery diarrhoea in children and neonates. Virulence via localized adherence to enterocytes. Infection usually self-limiting.
- **Enterotoxigenic *E. coli* (ETEC)** Affects children in developing countries, and travellers. Binds to enterocytes and produces heat-labile or heat-stable toxins, causing watery diarrhoea. Antibiotics not usually needed, though effective therapy (e.g. quinolone) given early shortens duration of illness.
- **Enteroinvasive *E. coli* (EIEC)** Rare cause of dysentery. Resembles ➔ *Shigella*.
- **Enterohaemorrhagic *E. coli* (EHEC)** Important invasive pathogen, responsible for 15–35% of haemorrhagic colitis: *E. coli* 0157 associated with ➔ haemolytic–uraemic syndrome (HUS) through production of shiga-like toxins. Most common vehicle is hamburger meat. Incubation period 1–14d. Antibiotics may ↑ risk of HUS.
- **Enteroaggregative *E. coli* (EAggEC)** Common cause of traveller's diarrhoea, and persistent diarrhoea in children and HIV-infected individuals. Usually self-limiting, but sensitive to fluoroquinolones and azithromycin if protracted.
- **Diffusely adherent *E. coli* (DAEC)** Possible cause of gastroenteritis, but pathogenicity not confirmed (some consider organism part of normal bowel flora).

Exclusion diets

Systematic exclusion of different foods and use of symptom diary can help identify foods to which patient may be intolerant or allergic (see also ➔ food allergy). True elimination diet difficult to pursue and should ideally involve help of experienced dietician. Involves 'washout period' of taking bland food such as boiled rice, fish, and chicken over 3–4d, followed by re-introduction of a favourite food every day. About 30% of patients with ➔ irritable bowel syndrome can identify foods that aggravate symptoms (see also ➔ FODMAP diet). Rarely a single dietary element that causes problems, and typically avoidance of several components required.[7]

Extracorporeal shock-wave lithotripsy (ESWL)

See: ➔ Lithotripsy.

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[7] Lomer MCE *et al.* (2015). *Aliment Pharmacol Ther* **41**: 262–75.

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Fabry's disease

Pathogenesis and epidemiology

X-linked disorder of glycolipid metabolism due to deficiency/absence of α-galactosidase A. Sphingolipid deposition occurs in all tissues, resulting in inflammation, ischaemia, hypertrophy, and fibrosis. Prevalence 1:117,000 (1:50,000 ♂).

Clinical features

Classic presentation with cutaneous angiokeratomas, cardiomyopathy, and renal failure. GI symptoms common, particularly dysmotility, leading to recurrent cramping, abdominal pain, and watery stools. ➲ Bacterial overgrowth and delayed gastric emptying can occur. Electron microscopy show lipid-filled vacuoles in ganglion cells of Meissner's plexus and endothelial cells. Lipid deposition in small vessels can lead to vasculitis and thrombosis. Mucosal enterocytes normal.

Diagnosis

Principally made by determination of enzyme activity in plasma or WBCs. Molecular gene analysis available. Refer for family screening and genetic counselling if index case identified.

Treatment

Mostly symptomatic. Enzyme replacement therapy delays/prevents progression of disease, but little reversal of established pathology.[1]

Faecal incontinence

See: ► Approach to faecal incontinence.

Faecal occult blood tests (FOBT)

See ➢ 'Faecal occult blood tests (FOBT)', p. 152.

Familial adenomatous polyposis (FAP)

Aetiology and pathogenesis

Most common adenomatous polyposis syndrome (others include ➲ juvenile polyposis, and ➲ Peutz–Jeghers, ➲ Gardner's, and ➲ Turcot's syndromes). Autosomal dominant, with prevalence 1/7,500, and 80–100% disease penetrance. APC (adenomatous polyposis coli) gene located on chromosome 5 encodes for protein that functions as tumour suppressor, probably through interaction with β-catenin. If the APC protein is mutated, β-catenin is no longer down-regulated, allowing it to up-regulate target genes that then promote adenoma formation.

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[1] Carubbi F & Bonilauri L (2012). *Intern Emerg Med* **7** (**Suppl 3**): S227–31.

Clinical features

Patients may present with rectal bleeding and diarrhoea, but many identified for screening/surveillance on basis of careful family history from affected index case (nevertheless, 20% of patients with FAP have no family history, suggesting sporadic germline mutation).

Colonic disease

Hundreds of adenomatous ➲ colonic polyps may develop after puberty, and diagnosis is usually made at age 20–30y. ➲ Colonic cancer inevitable part of disease course ~10–15y after onset of polyposis. 90% of cases of FAP diagnosed at age <50y.

Gastroduodenal disease

Duodenal adenomas occur in 60–90%, and duodenal/periampullary cancers in 5–12% (Plate 20). Following widespread use of prophylactic colectomy, duodenal cancer is now the major cancer presentation. Spigelman classification assesses duodenal FAP according to number, distribution, and histology of polyps. Endoscopic assessment (with duodenoscope rather than gastroscope in view of periampullary involvement) ± endoscopic US advised every 1–3y following colectomy or if >20y of age. The very poor prognosis following radical surgery in FAP patients with duodenal carcinoma, and >30% risk of developing cancer in those with Spigelman IV disease, has led most specialist units to advise prophylactic ▷ Whipple's resection for extensive pre-malignant duodenal FAP. ➲ Gastric polyps common, but ➲ gastric cancer rare.

Cancer in other sites

Although less common than luminal GI cancers, other associations include ➲ pancreatic cancer, hepatoblastoma, diffuse mesenteric fibromatosis (desmoid tumours), and cancers of the thyroid and brain.

Investigation

In an affected individual with no family history, diagnosis is suggested by finding hundreds of adenomatous polyps on lower GI endoscopy. Most <1cm, and individually are identical to adenomatous polyps found in general population.

Management

- Where diagnosis is established, there is no specific merit in waiting before advising colonic resection in post-pubertal patient in view of near certainty of developing malignancy.
- Colectomy with ileorectal anastomosis maintains continence, but cancer recurrence in rectal stump in 15%, even with regular surveillance, and carries dismal prognosis. Colectomy with ileoanal pouch formation, or total colectomy with ileostomy, usually advised.
- In cases where an ileoanal pouch is formed, annual pouchoscopy advised to screen for ileal adenomas.
- Polyp regression shown with sulindac (may act via COX-2 inhibition), but reliable prevention of progression to malignancy not shown and medical management cannot be used in place of surgery. Can reduce development of new polyps in rectal stump. Role in inducing regression of gastroduodenal polyps under assessment.

Screening

Genetic diagnosis of APC mutation can be made in >98% of patients using exhaustive genetic techniques. Commercially available 'truncated protein test' will be positive in 80% of FAP families. Where it is in a family member, gene carriage of other family members can be demonstrated with near 100% accuracy. A negative test in a family member removes the need for regular surveillance, but in those tested positive, sigmoidoscopy should be performed yearly from age 10–12y. If the affected family member is negative on genetic testing, screening relies on clinical assessment (i.e. sigmoidoscopy). Genetic counselling is a vital component of screening.

Familial Mediterranean fever (FMF)

Epidemiology and pathogenesis

Autosomal recessive disease. Affects up to 1:500 in high prevalence populations (e.g. Sephardic Jews, Armenians). Caused by mutations in *MEFV* gene (chromosome 16): encodes pyrin, expressed in neutrophils and part of inflammasome; mutations lead to ↑ IL-1β production.[2]

Clinical features

Symptoms begin at <20y in >95% of cases. Recurrent episodes of fever, peritonitis (mimicking acute abdomen), pleurisy, arthritis, and rash. Episodes last 24–72h. Serum amyloid A deposition may lead to renal failure. Presents to gastroenterologists with unexplained recurrent attacks of pain (often with 'negative' laparotomies). See ▲ **Acute abdominal pain** ▲.

Investigations

- ↑ Acute phase response (ESR, CRP) and neutrophilia.
- Genetic analysis. Diagnosis primarily clinical, but may be supported by genetic testing. Identification of common MEFV mutations, in individuals with typical clinical manifestations, obviates role for 'trial of colchicine'.

Management

Colchicine 1–2mg/d PO markedly effective in >95% of cases, and may prevent development of ➔ amyloidosis. In patients who appear not to respond, firstly suspect non-concordance. If truly resistant, anti-IL-1 therapies (anakinra, canakinumab, and rilonacept) available. See also Cochrane Review, 2015 🖱 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010893.pub2/abstract.

Familial pancreatitis

See: ➔ Hereditary pancreatitis.

Fat malabsorption

See: ► Approach to malabsorption and steatorrhoea.

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[2] Ozen S & Bilginer Y (2014). *Nat Rev Rheumatol* **10**: 135–47.

Felty's syndrome

First 5 cases described in 1924 by American physician Augustus Felty in *Johns Hopkins Medical Bulletin*. Combination of rheumatoid arthritis, splenomegaly, and neutropaenia. Relevant to gastroenterologists as >50% have abnormal liver histology, ranging from portal fibrosis to ➔ nodular regenerative hyperplasia. Can cause ➔ portal hypertension and variceal bleeding. Treatment primarily directed at underlying rheumatoid arthritis. May need G-CSF support if neutropaenia profound and associated with severe infection. Splenectomy can correct portal hypertension if due to ↑ splenic blood flow.

FIB-4 index

Marker of hepatic fibrosis. Calculated as $(\text{age}*\text{AST})/(\text{plt}*\sqrt{\text{ALT}})$ 🖱 http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4. Good predictive accuracy for advanced fibrosis in NAFLD, and HCV positive patients (Box 4.21).[3]

Box 4.21 Interpretation of FIB-4 index

- **NAFLD:**
  - FIB-4 score <1.3 = F0–F1.
  - FIB-4 score >2.67 = F3–F4.
- **HCV:**
  - FIB-4 score <1.45 = F0–F1.
  - FIB-4 score >3.25 =F3–F4.

*METAVIR fibrosis score: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; F4, cirrhosis.

Fibre

Refers to food residue, usually from structural and matrix components of plant cell walls, resistant to hydrolysis by digestive enzymes. Some fibre can bind ions (calcium, iron, magnesium, zinc) and adsorb bile salts, proteins, and bacterial cells. Fermentation by bacteria generates ➔ short-chain fatty acids, a preferred energy source for colonocytes.

Water-insoluble fibre (present in oats, fruit, beans, pulses, root vegetables) has greater effect on stool mass than water-soluble (present in cereals, nuts, seeds, fruit/vegetable skins). Water-soluble fibre (also known as fermentable or degradable fibre) stimulates bacterial growth and generates faecal mass largely composed of bacteria.

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[3] Sterling RK *et al.* (2006). *Hepatology* **43**: 1317–25.

Effects on GI tract

Affects GI motility: gums and pectins slow gastric emptying, while particulate fibres like wheat bran appear to increase it. Effect on intestinal transit time depends on particle size and bulk-forming capacity; large particle size (e.g. coarse bran) more effective than small particles in speeding colonic transit. ↑ fibre intake has been proposed to ↓ incidence of various diseases including ➔ colonic cancer, ➔ diverticular disease, ➔ appendicitis, ➔ cholelithiasis, constipation, and haemorrhoids. Bulk of evidence supports high-fibre diet but direct protective effect against colon cancer or in preventing adenoma recurrence not proven. Government guidelines suggest minimum daily fibre intake of 30g for adults. However, current average is insufficient at ≈18g.

Fissures

See: ➔ Anal fissure.

Fistulae

See: ➔ Anorectal fistulae.

Flukes (flatworms, trematodes)

Intestinal flukes

The 3 common intestinal flukes are *Fasciolopsis*, *Heterophyes*, and *Echinostoma*. These tend to be geographically restricted (Asia, Indonesia). People are infected by eating fish or freshwater plants infected with metacercariae. *Fasciolopsis* can be up to 7.5cm long; *Heterophyes* and *Echinostoma* only a few millimetres. Symptoms correlate with worm burden: often minimal but may include abdominal cramps, diarrhoea, and malabsorption (in heavy infections). Potential to migrate through circulatory and lymphatic systems. Diagnosis in all cases involves finding eggs in stool. Treatment with praziquantel 25mg/kg tds for 1d.

Liver flukes

Liver flukes include ➔ *Clonorchis*, *Opisthorcis*, *Fasciola*.

- ➔ *Clonorchis* and *Opisthorcis* endemic to SE Asia (one species found in Russia/Ukraine). Infection occurs by eating metacercariae in undercooked fish. Worms grow into adults in biliary tree and can cause ➔ cholangitis, ➔ biliary strictures, ➔ gallstones, and ➔ liver abscesses. The most important complication is ➔ cholangiocarcinoma. Diagnosis by stool microscopy, supplemented where available with molecular identification techniques. Treatment with praziquantel 25mg/kg tds for 3d.
- *Fasciola* similar to ➔ *Clonorchis* and *Opisthorchis* but has worldwide distribution, larger (up to 7cm), and frequently asymptomatic. Long life span (up to 14y). Four clinical phases recognized: incubation, invasion, maturation, and chronic biliary obstruction. During migration phase,

flukes traverse from intestine into liver across peritoneal cavity or up bile ducts, and can cause abdominal pain ± hepatomegaly. Chronic phase marked by intermittent biliary obstruction ± cholangitis. Typically diagnosed during 2nd or 4th phase. Eosinophilia often present. Stool microscopy can reveal eggs, though shedding can be low, limiting sensitivity. Serum ELISA highly sensitive and specific. CT may show hypodense nodular areas from parasite deposition or tunnel-like branching hypodensity from parasite migration through liver. If diagnosis remains in question, laparoscopy with biopsy can show characteristic yellow-white hepatic nodules in serpiginous configuration, with histology typically showing eosinophilic inflammatory infiltrate, granulomas, and Charcot–Leyden crystals. Resistant to praziquantel, so triclabendazole 10mg/kg single dose is the drug of choice.[4]

Blood flukes

Include ➲ schistosomiasis.

Focal nodular hyperplasia (FNH)

- Most commonly found in ♀ aged <40y. Incidental in majority.
- Non-specific abdominal pain in 15%. Rarely, spontaneous haemorrhage. No clear link with exogenous oestrogens, in contrast with ➲ hepatic adenomas. Thought to arise as hyperplastic, regenerative response to pre-existing vascular malformation in centre of nodules.
- Usually solitary. On CT, central hypodense scar and vascular enhancement with IV contrast are characteristic. Most lesions <5cm, with histology resembling cirrhosis (but normal surrounding parenchyma) and central stellate scar often containing thick-walled blood vessels.
- Surgical resection rarely required, but may be indicated if significant symptoms clearly attributable to FNH, if there are any complications (e.g. haemorrhage), or if there is doubt about the diagnosis.

FODMAPs

A diet low in certain fermentable food groups was designed specifically to treat ➲ irritable bowel syndrome in 1999; subsequent studies have demonstrated its benefit. Premise is that some fermentable foods can cause diarrhoea (due to their osmotic effect), while others drive colonic bacterial gas production, resulting in bloating and pain. It therefore has greater rationale in patients with bloating, pain, or diarrhoea-predominant IBS, and is less appropriate for those with constipation predominating. If available, preferable that a dietitian administers advice and supervises the diet. The low FODMAP diet begins with elimination of all FODMAPs (see Box 4.22) for 6–12wk, followed by gradual reintroduction until patients reach tolerable intake.

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[4] Ashrafi K *et al.* (2014). *Travel Med Infect Dis* **12**: 636–49.

Box 4.22 FODMAP food groups

- **F**ermentable
- **O**ligosaccharides (e.g. fructans, galactans)
- **D**isaccharides (e.g. lactose)
- **M**onosaccharides (e.g. glucose, fructose)
- **A**nd
- **P**olyols (e.g. sorbitol, mannitol, maltitol, xylitol, and isomalt).

Examples of high FODMAP foods include onion, garlic, pulses, brassicas (cabbage, cauliflower, broccoli), stone fruits (plums, peaches, nectarines, apricots), dairy products (if lactase deficient), and some sweeteners (if contain sorbitol or fructose corn syrup).

Folic acid (vitamin B_9)

- Complex pterin molecule conjugated to glutamic acid. Cannot be synthesized in body, therefore must be acquired in diet. Water-soluble. Found in dark green vegetables (e.g. spinach, beans), liver, and peanuts. Destroyed by prolonged cooking.
- Primarily absorbed in duodenum and jejunum.
- Functions as donor of 1-carbon groups, essential for synthesis of nucleic acid, proteins, acetylcholine, and methionine.
- Recommended intake 200mg/d. Uptake by specific carrier-mediated process that involves a hydrolase.

Folate deficiency

Causes

- Inadequate dietary intake.
- Impaired absorption:
  - Alcohol. Inhibits hydrolase which may contribute to deficiency seen in chronic alcohol dependence.
  - Zinc deficiency. Required to activate mucosal conjugase.
  - Small intestinal mucosal disease (e.g. ➔ coeliac disease, ➔ bacterial overgrowth, ➔ short bowel syndrome, ➔ tropical sprue, ➔ Whipple's disease).
- Increased requirements (e.g. pregnancy).
- Drugs: methotrexate, pyrimethamine, trimethoprim, triamterene, sulfasalazine (inhibits transport), phenytoin, carbamazepine.

Clinical features

Consequences of deficiency include megaloblastic anaemia, peripheral neuropathy (predominantly sensory), glossitis, and cognitive deficits. These features may correlate incompletely with each other. There is also ↑ risk of neural tube defects in children born to ♀ with folate deficiency. Most guidelines recommend that all women planning pregnancy take supplements of 400μg/d, starting ≥4wk before conception, and that those at high risk take 5mg/d, for ≥12wk.[5]

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[5] Cawley S *et al.* (2016). *Eur J Clin Nutr* **70**: 143–54.

Diagnosis

- FBC may show anaemia with macrocytosis (↑ MCV), due to megablastic changes (confirmed on blood film). If concurrent iron deficiency, MCV can be normal as mixed microcytic and macrocytic picture; this will be reflected as ↑ RDW.
- Assays available for both serum and RBC folate.
  - Measurement of serum levels requires fewer analytical hurdles, and is sensitive to dietary intake. Reference range 2.5–20ng/ml.
  - RBC folate provides more accurate representation of long-term status. Should be >140ng/ml if replete.
  - Serum testing generally sufficient unless strong clinical suspicion of deficiency despite normal serum folate and vitamin B_{12} levels.
- Plasma homocysteine concentrations sometimes used as non-specific indicator of functional folate status. Reference range 5–16mmol/L. Elevated in both folate and B_{12} deficiency, but can be paired with methylmalonic acid measurement (normal range 70–270mmol/L), which is only ↑ in B_{12} deficiency.

Treatment

- Address underlying cause, if possible.
- Supplement with 5mg PO daily.
- If concurrent ➔ vitamin B_{12} deficiency, ensure this is corrected first, otherwise risk precipitating subacute combined degeneration of spinal cord (restoring folate further drives B_{12} consumption).
- Treat for at least 6mo. Improvement in neurological symptoms and signs is typically slow, and may not be fully reversible.

Food allergy (food intolerance)

- Food allergy implies an immune-mediated reaction to certain foods. Food intolerance is a better term for non-immune reactions and, among adults, is more common than allergy.
- Food intolerance can be enzymatic (e.g. lactose intolerance due to congenital or acquired lactase deficiency), pharmacological (e.g. sensitivity to vasoactive amines such as tyramine in cheeses), or idiopathic.
- Prevalence of true food allergy is up to 8% in children <3y, with ≈2.5% of infants under 2y having cow's milk allergy.
- Many allergies recede after 1st decade and rates among adults ≈2.5%. However, this is increasing. In last decade, cases of food allergies have doubled and number of hospitalizations caused by severe allergic reactions ↑ 7-fold.
- Food allergy is the most common cause of anaphylactic reactions. Peanut allergy is most common and has prevalence of 0.5–7% in adults. Allergies to cow's milk, eggs, and seafood also common.
- Risk factors include immature mucosal immune system, early introduction of solid food, IgA deficiency, and inadequate challenge of mucosal immune system with commensal flora.
- Pathogenesis of true food allergy in most cases thought to involve failure of tolerance mediated by gut-associated lymphoid tissue. Both IgE- and cell-mediated process can occur.

Food poisoning

Majority (~75%) caused by bacteria, but can also be due to parasites (➲ *Giardia*, ➲ *Cryptosporidium*, trichinosis), viruses (e.g. ➲ hepatitis A) or chemicals (e.g. mushrooms). Common organisms shown in Table 4.14; most discussed under separate entries. In some cases, ➲ eosinophilic gastroenteritis may be manifestation of cell-mediated hypersensitivity to food antigens.

Forrest classification of GI bleeds

See: ➲ Scoring systems for predicting outcomes in GI bleeds.

Fundoplication

See: ▷'Antireflux procedures', p. 181.

Table 4.14 Bacterial causes of food poisoning

➲ *Salmonella*	>50% confirmed cases.
Enterotoxigenic ➲ *E. coli* (ETEC)	Usually food-borne, short (<4h).
Staphylococcus aureus	Transmitted to food by humans. Outbreaks often happen when food kept warm so organisms multiply. Toxins heat-stable and if ingested produce symptoms in 1–6h. Growth favoured in food with high salt or sugar content.
➲ *Clostridium perfringens*	Spores in meat, 8–22h.
➲ *Shigella*	Diarrhoea (with blood in 25–50%), occurring within 1–3d, with fever and abdominal pain.
➲ *Clostridium botulinum*	Occurs due to ingestion of incorrectly preserved foods. Presents with a combination of abdominal and neurological symptoms and signs.
Vibrio cholerae (➲ Cholera) and *V. parahaemolyticus*	Common in less economically developed countries but rare elsewhere. Profuse diarrhoea ('rice-water') with subsequent dehydration and electrolyte depletion.
Bacillus cereus	Two different syndromes caused by different toxins: **Diarrhoea syndrome** has incubation period 6–14h, lasts ~24h, and probably depends on bacterial division *in vivo* after ingestion from variety of contaminated food. **Vomiting syndrome** has short incubation period (2h), diarrhoea in only 30%. Illness lasts 9h; classically comes from contaminated rice in Chinese restaurants.
➲ *Campylobacter*	Caused by raw/undercooked poultry, resulting in diarrhoea, abdominal pain, and fever.
➲ *Yersinia*	Caused by contaminated meats or milk. Results in diarrhoea (can be bloody), pain, and fever.
➲ *Listeria*	GI illness can rarely be complicated by sepsis or meningitis.

Section 4

G

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Gallbladder cancer

Epidemiology

Rare malignancy, usually affecting older patients. Often presents at advanced stage when curative treatment not possible. Associated with ➲ gallstones in 70–90% of cases, calcified ('porcelain') gallbladder (gallbladder cancer in 25%), and ➲ gallbladder polyps >1cm in diameter (malignant in 23–88% of patients). In ➲ primary sclerosing cholangitis, gallbladder polyps (even <1cm) are a risk factor for malignancy. Tumour is in gallbladder fundus in 60%, body in 30%, and neck in 10%.

Clinical features

Symptoms often vague in early stages. RUQ discomfort, weight loss, and jaundice occur in late stages. Hard tender mass sometimes felt in region of gallbladder. Incidental finding of gallbladder cancer in 1–3% of cholecystectomies performed for gallstones.

Investigations

US, contrast-enhanced CT, or MRI may show thickened gallbladder wall and irregular mass within gallbladder lumen. Local spread (usually into adjacent liver) is well shown with CT. In jaundiced patient, ERCP may allow both biliary decompression and stricture sampling. PET-CT can evaluate distant spread, but has little additional role in clinical practice beyond high-resolution CT. Percutaneous biopsy may allow histological diagnosis, but not performed in patients deemed to have surgically curable disease due to risk of needle track seeding.

Management

Surgery is the only potentially curative option. Usually involves cholecystectomy ± bile duct, adjacent liver, and local lymph node resection. 1st line palliative chemotherapy gemcitabine + cisplatin after UK-ABC-02 study demonstrated survival benefit compared to gemcitabine alone (11.7 vs. 8.1 months).[1] No standard 2nd line therapy, but novel agents and targeted therapies (e.g. erlotinib, an EGF receptor inhibitor) undergoing evaluation. Maintaining biliary drainage crucial determinant of survival, with percutaneous or endoscopic biliary stenting (Plate 41). Overall mean survival 6 months; 5-year survival <5%.

Gallbladder empyema

Refers to pus within gallbladder. Usually develops following acute ➲ cholecystitis, but cystic duct obstruction due to tumour (e.g. ➲ cholangiocarcinoma) may also occur. Infection may arise from ➲ cholangitis. Usually presents with RUQ pain and sepsis. Gallbladder perforation with subsequent peritonitis is an important complication if left untreated. CT or US may show distended, fluid-filled gallbladder with pericholecystic fluid. Treatment is with IV antibiotics to cover Gram-negative organisms and anaerobes (e.g. 3rd generation → CEPHALOSPORIN and → METRONIDAZOLE) + percutaneous gallbladder drain insertion (cholecystostomy). Cholecystectomy usually delayed by 4–6wk because of high rate of postoperative septic complications.

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[1] Valle L *et al.* (2010). *N Engl J Med* **362**: 1273–81.

Gallbladder polyps

- Refers to any mucosal projection into gallbladder lumen. Prevalence 1–4%. More than 90% are not neoplasms at all (e.g. cholesterol 'polyp' arising from gallbladder wall), and <5% are true adenomas. Difficult to define different types accurately on imaging (usually US), but malignant change very rare in any polyp <10 mm. Exception is patients with ➔ primary sclerosing cholangitis, in whom small studies show adenocarcinoma in 60% of polyps, even if <1cm.
- Usually asymptomatic, or found in association with symptomatic ➔ gallstones.
- Prudent management is to perform ➤ cholecystectomy if polyp >10mm (and certainly if >18mm, as these carry significant risk of invasive adenocarcinoma), or if symptomatic/associated with gallstones. In those with polyps <10mm, 6–12 monthly US may be considered to exclude increasing size.

Gallstones

Epidemiology and pathogenesis

Present in 10–20% of adults. Higher prevalence in ♀, 1st-degree relatives of sufferers, obesity, and pregnancy. Other risk factors include:

- Terminal ileal disease, including ➔ Crohn's disease and surgical resection (possibly due to ↓ bile acid absorption, ↑ cholesterol:bile acid secretion, and supersaturated bile).
- Haemolysis (e.g. ➔ sickle cell anaemia). pigment stones.
- Chronic biliary infection (e.g. ➔ *Clonorchis*).

Cholesterol-predominant stones account for 75%; pigment stones (calcium bilirubinate, mucin glycoprotein, bacterial products) for remainder.

Clinical features

Range of clinical scenarios, and pattern determines specific investigations and management. Symptoms develop in 1–3% of patients/y.

Asymptomatic gallstones

Up to 80% of individuals with gallstones remain asymptomatic, with incidental diagnosis made on imaging.

Symptomatic gallstones

- Biliary colic refers to 1–5h of constant severe, dull, or boring pain, most commonly in epigastrium or RUQ. Often triggered by eating (especially fatty foods). Pain may radiate to right scapular region. Severe biliary colic occurs in 1–8%/y, and other complications (e.g. ➲ acute pancreatitis, ➲ cholecystitis) in 1–3%/y.
- Acute ➲ cholecystitis presents with biliary colic-type pain, but lasts hours to days. Often associated with nausea, vomiting, and fever.
- Jaundice and RUQ pain suggest ➲ choledocholithiasis, or more rarely ➲ Mirizzi's syndrome. Evidence of sepsis points to ➲ cholangitis.
- ➲ Acute pancreatitis can occur as result of passage of stones into common bile duct (see ➲ choledocholithiasis).

Investigations

Imaging

- Transabdominal US >92% sensitive and 99% specific for gallbladder stones >2mm, and usually only modality required. Much less sensitive (~50%) at detecting common bile duct (CBD) stones but gives good indication of duct dilatation if obstructed.
- AXR rarely of use as only 10% of gallstones radiolucent.
- CT scanning may miss 20% of gallbladder stones, but effective in detecting complications of cholecystitis (e.g. perforation, empyema).
- MRCP indicated if moderate/high suspicion of CBD stones not seen with US.
- EUS highly accurate in detection of gallbladder stones or sludge, but invasive and rarely necessary in uncomplicated cases. Comparable with MRCP for CBD stones.

Blood tests

- LFTs normal unless stones obstructing biliary tree.
- Against expectation/logic, acute biliary obstruction by stones often manifests with raised transaminases (↑ ALT/AST), rather than predominant cholestasis (↑ ALP/γGT).
- See also ➲ cholecystitis, ➲ choledocholithiasis, ➲ cholangitis, ➲ gallbladder empyema.

Management

Cholecystectomy not indicated for asymptomatic gallstones, but required for symptomatic disease (see ➲ cholecystitis, ➲ choledocholithiasis), assuming patient is surgically fit.

Gardner syndrome

Familial disease consisting of inherited colonic adenomatous polyposis and extracolonic lesions. Latter may include osteomas, dental abnormalities, congenital hypertrophy of retinal pigment epithelium, desmoids, epidermoid cysts, fibromas, lipomas, and/or adrenal adenomas. Syndrome now considered subset of ➲ familial adenomatous polyposis (FAP), as both arise from mutations in *APC* gene.

Patients at ↑ risk of both colonic and extracolonic malignancies (arise in <5%, and may affect duodenum, thyroid, pancreas, liver, or biliary tree). No consensus on optimum screening strategy, but at minimum should undergo same screening as patients with FAP.

Gastric antral vascular ectasia (GAVE)

Vascular disorder of gastric antrum, characterized by tortuous dilated blood vessels radiating proximally from pylorus. Also called 'watermelon stomach'. Associated with ➲ portal hypertension in 30%, and with autoimmune disease (e.g. Sjögren's syndrome, atrophic ➲ gastritis). Focal capillary thrombosis with dilated submucosal venous channels and fibromuscular hyperplasia of muscularis mucosa found histologically, but diagnosis made on endoscopic appearance. May cause ▲ **acute upper GI bleeding** ▲ or, more commonly, chronic iron-deficiency anaemia. Iron therapy and transfusions may be required. Endoscopic therapy with laser photocoagulation, ▹ argon plasma coagulation and heater-probe increasingly used. Although correlation with portal pressures is poor, patients with cirrhosis and GAVE usually have more severe liver disease. Not an indication for ➲ TIPPS.

Gastric cancer

Definition and epidemiology

- Adenocarcinoma accounts for >90% of gastric neoplasms (others include ➲ lymphoma, ➲ gastrointestinal stromal tumour, and ➲ carcinoid). Despite ↓ incidence over last 30y (particularly in West), remains 3rd most common cancer worldwide. Large geographical variation, with highest incidence in Far East. Most patients >60y.
- Adenocarcinoma differentiated by gross appearance and histological type: tubular, papillary, mucinous or signet-ring cells, or undifferentiated. Lauren system classifies gastric adenocarcinoma as type I (intestinal) or type II (diffuse: linitis plastica).
  - **Diffuse form** more common in ♀, occurs at younger age, and carries particularly poor prognosis.
  - More common **intestinal form** closely linked to environmental factors.
  - Third 'metabolic' subtype has been described that preferentially responds to 5-FU.[2]
- Early gastric cancers ('EGC'), mainly reported in Japan (≈35% of cases), defined as tumour not extending beyond mucosa.

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[2] Lei Z *et al*. (2013). *Gastroenterology* **145**: 554–65.

Aetiology and pathogenesis

- Combination of genetic and environmental factors important. 10% of cases exhibit familial clustering. Mutations of p53 tumour suppression and APC genes appear important in tumour development.
- **Risk factors** include ➲ *Helicobacter pylori* (probably predisposes by inducing ➲ atrophic gastritis, and classified by WHO as class 1 carcinogen), smoking, high intake of salted and/or preserved foods, ➲ familial adenomatous polyposis (10× risk of gastric cancer, related in part to gastric adenomas, found in >30%), ➲ hereditary non-polyposis colorectal cancer (11% chance of gastric cancer), ➲ Ménétrier's disease, ➲ pernicious anaemia, atrophic gastritis, post-partial gastrectomy, high grade dysplasia on biopsy, and ➲ gastric polyps >1.5cm.
- Distribution of cancer within stomach: 40% antral, 35% in body, 15% in fundus/cardia, 10% diffuse. Overall ↓ in gastric cancer particularly relates to distal tumours, but proximal lesions may be increasing (see also ➲ oesophageal tumours). Commonly metastasizes to liver (40%), lung, bone marrow, and/or peritoneum.

Clinical features

Usually presents late, with epigastric discomfort, weight loss, anorexia, nausea, early satiety, upper GI bleeding, or symptoms of anaemia. Symptoms may be indistinguishable from ➲ peptic ulceration. Vomiting may relate to pyloric obstruction, and tumour bulk may give early satiety. On examination, palpable epigastric mass may be found.

Investigation

- Blood results non-specific (no reliable tumour markers), but iron-deficiency anaemia may be present.
- Upper GI endoscopy most useful diagnostic tool. Tumour may have appearance of benign gastric ulcer (repeat endoscopy and biopsies until resolution of even 'benign-looking' gastric ulcers is essential), polypoid mass, or diffuse gastric wall involvement.
- CT scanning is the main imaging modality for assessing local and distant spread, and surgical resectability.
- EUS allows determination of depth of invasion with 80% accuracy. Gastric cancers usually staged according to TNM classification (see ➲ tumour staging); >90% accurate at distinguishing between stage T1 and T2, so is the best modality for distinguishing early from advanced cancer. EUS required as adjunct to CT in only a minority of cases. May be limited by stricturing disease, and operator dependent.
- PET has increasing role in detecting lymph node metastases.
- Combined imaging of CT, EUS, and PET-CT provides highest yield for identifying nodal involvement.

Management and prognosis

- Surgery provides only hope of cure for locally advanced disease. Optimal approach (e.g. total gastrectomy/subtotal gastrectomy, role of splenectomy, and extent of lymph node resection) is debated.
- Endoscopic mucosal resection (EMR) curative for EGC confined to mucosa (particularly common in Japan). Should be limited to those with solitary small tumours (<2cm) and no evidence of extension beyond mucosa on imaging, including EUS.

- Gastric adenocarcinoma is poorly responsive to chemotherapy or radiotherapy, but adjuvant chemoradiotherapy provides survival benefit. Range of regimens have been used (e.g. fluorouracil + folinic acid).
- EGC has 90% 5y survival, but overall 5y survival for gastric cancer in USA ~20%.

Guidelines

✍ British Society of Gastroenterology guideline for management of oesophageal and gastric cancer (2011).

Gastric lymphoma

See: ➔ Lymphoma in GI tract.

Gastric polyps

Found in 1–3% of all gastroscopies. Usually asymptomatic and benign, although large polyps can present with bleeding, anaemia, and abdominal pain. All polyps should, when possible, be biopsied to exclude malignancy. In cases with multiple polyps, largest polyp should be excised and biopsy samples taken as representative sample of the remaining polyps. Polyps can be snared using electrocautery; bleeding occurs as complication in ≈5%.

Hyperplastic polyps are the most common type (75%). Multiple fundic gland polyps can occur, and are not significant. Adenomas account for 10–20%, may progress to adenocarcinoma, and may occur in pernicious anaemia. Patients should have ➔ *H. pylori* eradicated, and surveillance due to risk of malignancy. Consider ➔ familial adenomatous polyposis in young, ➔ *H. pylori* negative patients. Risk of cancer related to polyp size and low in those <2cm diameter. Management depends on tumour type, size, and staging (Fig. 4.10).

Guideline

✍ British Society of Gastroenterology guideline for the management of gastric polyps (2010).

Gastric ulcers

See ➔ Peptic ulceration.

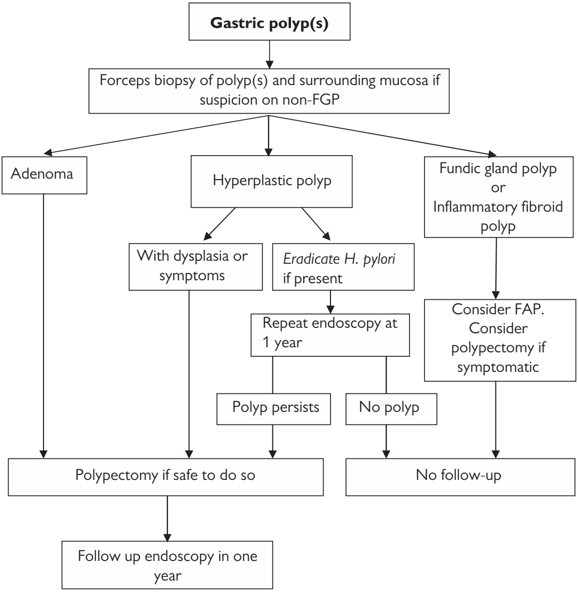
Gastric polyp(s)
Forceps biopsy of polyp(s) and surrounding mucosa if suspicion on non-FGP
Adenoma
Hyperplastic polyp
Fundic gland polyp or Inflammatory fibroid polyp
With dysplasia or symptoms
Eradicate H. pylori if present
Repeat endoscopy at 1 year
Consider FAP. Consider polypectomy if symptomatic
Polyp persists
No polyp
Polypectomy if safe to do so
No follow-up
Follow up endoscopy in one year

Fig. 4.10. Algorithm for management of gastric polyps. Reproduced with permission from Goddard AF *et al*. The management of gastric polyps. (2010) *Gut* **59**: 1270–6.

Gastrinoma

Background

- One of the most common types of ➔ neuroendocrine tumour. Incidence ~1/million. More than 90% occur in duodenum or pancreas. Unlike other ➔ pancreatic endocrine tumours, majority of gastrinomas are malignant. At presentation, pancreatic gastrinomas more likely to be >2 cm, and to have metastasized, than duodenal lesions. ➔ Multiple endocrine neoplasia (MEN) type 1 in 30%.
- Zollinger–Ellison syndrome (ZES) refers to triad of severe ➔ peptic ulceration, gastric acid hypersecretion, and gastrinoma.

Clinical features

- Upper abdominal/epigastric pain in 75%, related to ➔ peptic ulceration (ZES accounts for 0.1% of cases).
- Chronic diarrhoea (and steatorrhoea) in >70%.
- Large pancreatic primary/liver metastases may present with abdominal pain/palpable mass.

Investigation

- Consider diagnosis in 'unusual' PUD (e.g. recurrent multiple ulcers, ➲ *Helicobacter pylori* + NSAID-negative disease, jejunal ulcers).
- Endoscopy shows single/multiple duodenal ulcers and prominent gastric folds (may mimic ➲ Ménétrier's disease).
- Fasting serum gastrin level >1,000pg/ml highly specific for ZES (in absence of achlorhydria and chronic atrophic ➲ gastritis). Gastrin 115–1,000pg/ml due to range of causes, including gastrinoma (see Table 4.15 and ➢ 'Gut hormone profile', p. 148).
- Secretin provocation test performed if equivocal fasting gastrin (>200pg/ml ↑ in serum gastrin after secretin injection diagnostic and does not occur with other causes of raised gastrin levels).
- Hypercalcaemia suggests possibility of MEN-1.
- To localize primary and metastases, scintigraphy (e.g. Octreoscan) or ^{68}gallium-octreotate PET are sensitive (most gastrinomas are somatostatin receptor positive). With improved CT and MRI imaging these are being used less often unless detection of very small metastases would change management. EUS increasingly used for small lesions.

Management

- Management in specialist units advised. Aim to control acid secretion and resect primary tumour.
- High-dose → PROTON PUMP INHIBITORS (e.g. omeprazole 40–80mg/d or pantoprazole 80–160mg/d) effectively control hyperacidity in most patients.
- If localized pancreatic head/duodenal gastrinoma, curative surgical resection possible in majority of cases.
- Management of metastatic disease (present in 1/3 at presentation, often to liver) similar to that of other ➲ neuroendocrine tumours. Following resection of liver metastases, 5y survival of 85% reported, but cure in <30%.

Table 4.15 Causes of serum gastrin 115–1,000pg/ml

Gastrinoma	Vagotomy
PPIs (stop for >1wk prior to test)	Small bowel resection
Atrophic gastritis	Renal failure (impaired excretion)
Primary hyperparathyroidism (?linked to MEN-1)	Hyperlipidaemia (may interfere with gastrin assay)
➲ Gastric cancer	➲ Pyloric stenosis

Gastritis

Histological inflammation of the stomach correlates poorly with symptoms and endoscopic appearances. Some erosive and hyperplastic disorders may not be associated with much inflammation. Diagnosis requires biopsy: indications and protocol shown in Box 4.23.

Box 4.23 When and how to take gastric biopsies

Indications for biopsy

Gastric erosion or ulcer, thickened folds, gastric polyps or masses, possible ➲ *H. pylori*, possible diffuse chronic gastritis.

Biopsy mapping protocol

Take five biopsies: antrum (greater and lesser curve), incisura, and gastric body (greater and lesser curve).

Classification

No universally accepted system. Sydney system best, but complicated. A general classification is shown in Box 4.24.

Box 4.24 Classification of gastritis

Associated

- Atrophic gastritis.
- Caustic or ulcerative gastritis.

Immune-mediated/infective

- Infectious: viral, bacterial, ➲ *H. pylori*, fungal, parasitic.
- Granulomatous: ➲ Crohn's disease, ➲ sarcoidosis, TB, foreign bodies.
- ➲ Graft-versus-host disease.

Distinctive

- ➲ Eosinophilic gastritis.
- Lymphocytic gastritis.

Iatrogenic

- Aspirin/NSAIDs.
- Alcohol, cocaine.
- Radiation.

Miscellaneous

- ➲ Biliary reflux.
- Ischaemia.
- ➲ Hiatus hernia.
- ➲ Ménétrier's disease.
- Zollinger–Ellison syndrome.

Viruses

➲ Cytomegalovirus (CMV) may affect stomach. Biopsies reveal enlarged cells with 'owl eye' inclusion bodies. Herpesvirus can (rarely) produce multiple small raised ulcers. Biopsies show intranuclear inclusion bodies surrounded by haloes.

Bacteria

- Acute necrotizing gastritis is rare but dangerous. Association with alcohol binges, respiratory infections, AIDS, and infected peritoneal shunts. Mucosa appears thickened with greenish-black exudate. Treatment involves extensive resection and penicillin.
- Very rarely, stomach may be infected with TB (usually associated with pulmonary TB), actinomyces, or syphilis.
- Can get reactive gastropathy (acute erosive gastritis). Inflammation is not a major feature.

Atrophic gastritis

Histological diagnosis, requiring endoscopic biopsy. Findings include chronic inflammation with loss of gastric glands and replacement by intestinal-type epithelium and fibrous tissue. Two main causes:

- **Type A (autoimmune atrophic gastritis)** Mainly restricted to corpus, with antral sparing. Characterized by autoantibodies against parietal cells and intrinsic factor, leading to ➲ pernicious anaemia.
- **Environmental factors** usually produce multifocal gastritis. Examples include dietary factors (e.g. nitroso compounds produced by bacterial metabolism of dietary nitrates) and ➲ *Helicobacter pylori*. *Helicobacter*-associated gastritis results from release of bacterial and inflammatory toxic products, and can result in either antral-predominant or multifocal gastritis, with partial replacement of gastric-type epithelium by intestinal epithelium. Mucosal inflammation, and therefore atrophic gastritis, more marked with cagA-positive strains. Antral-predominant gastritis is commonly found in infected patients with peptic ulcers. Multifocal and autoimmune gastritis are associated with development of gastric carcinoma.

Gastroenteritis

See: entries under causative organisms; ► Approach to acute diarrhoea.

Gastrografin® (sodium diatrizoate)

High osmolality, water-soluble radiological contrast medium. Safer alternative to barium if suspect perforation when examining lower bowel or swallow. Caution if high risk of aspiration or ➲ tracheo-oesophageal fistula, as hyperosmolality can trigger pulmonary oedema.

Gastro-oesophageal reflux (GORD)

See: ► Approach to dyspepsia and gastro-oesophageal reflux.

Gastroparesis

Syndrome of symptomatic, objectively delayed gastric emptying, in absence of mechanical obstruction. Prevalence 5% in patients with type 1 diabetes, and 1% in type 2 diabetes (see ➲ diabetes and the GI tract). Many studies report disturbed motility in ≈40% of patients with functional dyspepsia, although relation to symptoms and therapeutic response to prokinetics are imperfect. Some evidence viral infections can also impair emptying. Causes outlined in Box 4.25.

Clinical features

Early satiety, nausea, vomiting, bloating, and upper abdominal pain (often induced by eating). May occur in context of systemic neurological or myopathic illness, so full examination essential.

Box 4.25 Causes of delayed gastric emptying

Mechanical obstruction

- ➲ Pyloric stenosis.
  - Adult hypertrophic pyloric stenosis.
  - Chronic benign ➲ peptic ulceration.
  - ➲ Gastric cancer.
  - ➲ Bezoars.
- Duodenal tumour.
- Pancreatic disease (e.g. ➲ pancreatic cancer, ➲ chronic pancreatitis).

Impaired motility

- Autonomic neuropathy:
  - ➲ Diabetes.
  - Shy–Drager syndrome.
  - Parkinson's disease.
- Infiltrative: ➲ Amyloidosis.
- Collagen vascular disease: ➲ Systemic sclerosis.
- Post-surgical: Vagotomy, ➢ Roux-en-Y anastomosis.
- Drugs:
  - Anticholinergics.
  - Opiates.
  - Tricyclic antidepressants.
  - Glucagon-like peptide-1 agonists (e.g. exenatide, liraglutide).

Other

- Post-viral (e.g. CMV).
- Trauma (e.g. head injury).
- ➲ Dermatomyositis.
- Pregnancy.
- Myotonic muscular dystrophy.
- Hypothyroidism.
- ➲ Anorexia nervosa.

Diagnosis

Based on combination of symptoms + demonstrating absence of gastric outlet obstruction/➔ peptic ulceration + delayed gastric emptying.

- **Blood tests** Screen for diabetes, thyroid dysfunction, and (if compatible clinical features) connective tissue disease.
- **Endoscopy** To exclude gastric outlet obstruction/ulceration.
- **Scintigraphy** Accelerated gastric emptying and functional dyspepsia can elicit symptoms similar to gastroparesis, so formal demonstration of delayed emptying recommended before instituting therapy. Most reliable method is to show gastric retention of solids at 4h. Medicines that delay gastric emptying should be stopped ≥48h before testing, and glucose control in diabetics optimized in advance.

Therapy

Gastric dysmotility can be difficult to treat.

- **Dietary therapy** Advise small, low fibre, low fat meals, 4–5×/d.
- → PROKINETICS:
  - → DOPAMINE RECEPTOR ANTAGONISTS 1st line. Metoclopramide 10–20mg PO tds preferred to domperidone (risk of extrapyramidal side-effects with former < that of prolonged QT with latter).
  - Erythromycin 250–500mg PO tds. Develop tachyphylaxis, so usually only short-term solution.
- ➔ **Enteral tube feeding** Oral route preferred for nutrition and hydration if at all possible, but in severe cases NG/NJ or PEG/PEJ may be required. Added advantage is that can also be used for venting gastric contents to relieve symptoms.
- In exceptional circumstances, gastric electrical stimulation considered. Symptom severity and gastric emptying shown to improve in diabetic, but not in other forms, of gastroparesis.

Guideline

American College of Gastroenterology guideline on management of gastroparesis (2013).

Giardiasis

Giardia lamblia is a non-invasive, flagellate protozoan. Common cause of malabsorptive diarrhoea. Global distribution. Zoonotic (reservoirs: deer and beaver). Infects children > adults. Infection follows cyst ingestion: can be water (not inactivated by chlorine) or food-borne, or person-to-person (oroanal intercourse particularly high risk, causing cyclic infections). Infecting dose as low as 10, and consistently occurs with >100, cysts. When swallowed, stomach acid dissolves cyst wall, releasing proliferative trophozoites that adhere to small bowel enterocytes.

Clinical features

Incubation period 8d. May be asymptomatic, or cause diarrhoea, bloating, nausea, 'sulphurous' belching and flatus, fatigue, weight loss, and fever. Severe cases develop fat malabsorption and vitamin B_{12} deficiency (correct rapidly following treatment, suggesting luminal rather than mucosal events causative). Most cases self-limiting within 3–6wk. Signs vary with immune response: hypogammaglobulinaemia associated with severe disease, although severity not ↑ in AIDS.

Diagnosis

Stool microscopy only 50% sensitive, rising to >90% if test 3 samples. Duodenal biopsy better (~80%), and may show ↓ villous height, crypt elongation and intraepithelial lymphocytosis (mimics ➲ coeliac disease, though usually less severe). Stool antigen or PCR most sensitive.

Treatment

Tinidazole 2g two doses (4d apart) or metronidazole 500mg tds for 10d (📖 Cochrane review 2012).[3] In pregnancy, use paromomycin 25–35mg/kg/d in 3 divided doses for 7d. Treatment failure rare, but if occurs consider reacquisition (oroanal intercourse significant risk factor), underlying immune deficiency (see ❗ Pitfall, next), and drug resistance. In event of persistent disease, reasonable to re-treat with 1st line agents, before switching to alternative drugs or combination therapy. Remember there is a high incidence of lactose intolerance following *Giardia* infection.

❗ Pitfall

Recurrent/persistent giardiasis should prompt consideration of immunoglobulin immunodeficiency (IgA deficiency, common variable immunodeficiency). In such cases, infection persists until IVIg started.

Gilbert's syndrome

Described by Nicolas Augustin Gilbert (1858–1927; French physician, so 'soft' G in pronunciation). Most common cause of hyperbilirubinaemia, found in 5–10% of Caucasians. Raised unconjugated bilirubin due to defect in promoter for uridine diphosphoglucuronate-glucuronosyltransferase-1A1 (*UGT1A1*) gene, responsible for bilirubin conjugation to glucuronic acid.[4]

Diagnosis often made on routine blood testing (↑ unconjugated bilirubin, usually <65µmol/L), with all other LFTs normal. Occasionally detected when intercurrent illness, stress, menses, or fasting leads to transient clinical jaundice (see ► Approach to recent-onset jaundice). Liver biopsy not required. Life expectancy normal, and no specific treatment needed; however, ↑ toxicity may occur with drugs such as irinotecan.

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[3] Pasupuleti V *et al*. (2014). *PLoS Negl Trop Dis* **8**: e2733.

[4] Erlinger S *et al*. (2014). *Gastroenterology* **146**: 1625–38.

GIST (gastrointestinal stromal tumours)

Aetiology and pathogenesis

Subset of mesenchymal GI tumours, previously classified as leiomyomas and leiomyosarcomas. Represent 3% of GI tumours. Intramural well-demarcated spherical masses arising from muscularis propria. May project intraluminally, with overlying mucosal ulceration. Malignancy not reliably predicted by tumour size (may be >30cm), and 10–30% malignant, with >40% of malignant GISTs metastasized by time of presentation. Usually arise from upper GI tract (stomach 70%, small bowel 20%).

Clinical features

Can be found incidentally, but may present with abdominal pain, GI bleeding, or palpable mass. Rarely present with luminal obstruction.

Investigation

- Endoscopy may show smooth mass with central ulceration.
- Endoscopic ultrasound (EUS) allows accurate assessment, including demonstration that tumour arises from muscularis propria.
- CT and barium meal/follow-through may also delineate mass.
- Histologically graded as benign, borderline, or malignant, with histology showing diffuse sheets of spindle cells. Immunohistochemical staining of biopsy specimens important, with expression of surface markers CD117 and CD34 characteristic, and vimentin expression in >90%. Correlates with malignancy include tumour size >4cm, irregular extraluminal border, and cystic spaces and echogenic foci within GIST. Presence of 2 or 3 of these features predicts malignancy with 80–100% confidence.

Management

- Surgical resection is the treatment of choice (but complete resection may not be possible due to tumour size).
- Imatinib, a tyrosine kinase inhibitor, has an important role in treatment of metastatic or non-resectable GISTs. In patients with unresectable GIST, 2y survival increases from 26% with conservative treatment to 76% with imatinib. Tumours often become unresponsive after two treatments with imatinib. Newer treatments for non-responsive cancers include sunitinib and, in advanced cases, regorafenib.
- In patients with malignant GIST, 5y survival post-surgery 30–35%.

Globus

Feeling of lump or tightness in throat. Not accompanied by dysphagia or odynophagia. May be worsened by dry swallowing and emotional stress. Common symptom in somatization disorder. No documented association with abnormalities of upper oesophageal sphincter. 90% report coincident heartburn, but finding of oesophagitis or significant GORD on pH testing rare. Perception of oesophageal stretch may be increased. Reassurance and addressing underlying psychological triggers helpful.

Gluten sensitivity

See: ➜ Coeliac disease.

Graft-versus-host disease (GvHD)

Aetiology and pathogenesis

Most common following allogeneic bone marrow transplant, when donor T cells recognize recipient antigens and attack host epithelium. Results in dysfunction of skin, GI tract, and liver. In acute GvHD, leukocyte and cytokine activation cause cascade of tissue damage. In chronic disease, dysregulated T cells produce TGF-β that stimulates tissue fibroblasts.

Clinical features

Four patterns recognized:

- **Acute** Occurs 21–100d post-transplant. High mortality.
- **Chronic** Occurs after 100d.
- **Late-onset acute** Occurs after day 100 but clinical features of acute disease. More common with reduced-intensity conditioning therapy.
- **Overlap** Features of both acute and chronic GvHD.

Acute GI GvHD

- Affects up to 60% of patients receiving allogeneic transplants. Involves small and large intestine > stomach and oesophagus.
- Presents with nausea, vomiting, anorexia, secretory diarrhoea and, in severe cases, abdominal pain ± haemorrhage. Mucosal injury also allows bacterial translocation to systemic circulation.
- Often clinically indistinguishable from other causes of GI dysfunction: conditioning regimen toxicity (can result in severe mucosal damage for up to 3wk), infection or adverse drug reactions (particularly mycophenolate mofetil: causes eosinophilic colitis).

Chronic GI GvHD

Frequently presents with dysphagia due to ➜ oesophageal strictures or webs. Oral involvement common, with xerostomia and mucositis. Lower GI symptoms can include those due to acquired ➜ lactose intolerance, ➜ bile acid malabsorption, and disrupted motility.

Hepatic GvHD

- Three presentations encountered:
  - Asymptomatic LFT derangement.
  - Slowly progressive cholestatic jaundice.
  - Acute hepatocellular injury (particularly when tapering immunosuppression).
- Jaundice is a poor prognostic sign.

Investigation

- Associated skin features, such as a pruritic (often palmoplantar) maculopapular rash, can give clue to diagnosis.
- Endoscopy and GI biopsy. May see mucosal erythema, erosion, and ulceration, although ≈⅓ macroscopically normal. In chronic disease,

white plaques can mimic candidiasis. Poor correlations between visual severity of mucosal injury, underlying histopathology, and clinical outcomes. Histology in acute GvHD shows epithelial cell apoptosis ('exploding' crypt cells) and intestinal crypt loss; in chronic disease, fibrosis, crypt distortion, mild inflammation in lamina propria and Paneth cell metaplasia are seen.[5]

- Liver biopsy may show bile duct damage and, eventually, ductopaenia. Hepatocellular necrosis rare. Not required if GvHD evident elsewhere.
- CT scanning in specialist hands can support diagnosis.[6]
- Ultimately remains diagnosis of exclusion, after consideration of infection (particularly viral: see ➔ cytomegalovirus, ➔ hepatitis B-D), neutropaenic enterocolitis, ➔ sinusoidal obstruction syndrome, iron overload, and other adverse drug reactions.

Management

- Acute GvHD treated with high-dose → CORTICOSTEROIDS, (e.g. methylprednisolone 0.5–2mg/kg/d IV), in addition to continuing original immunosuppressive prophylaxis.
- Chronic GvHD treated with → CICLOSPORIN and → CORTICOSTEROIDS. If non-responsive, further treatment challenging and relies on symptomatic management (diarrhoea usually responsive to → OPIATES and occasionally → 5-AMINOSALICYLATES) ± ↑ immunosuppression.

Guideline

British Committee for Standards in Haematology Guideline on diagnosis and management of acute graft-versus-host disease.

Granulomas

Organized collection of macrophages with surrounding palisade of lymphocytes. Formed when immune system attempts to wall off material recognized as foreign but which acute inflammatory response cannot eliminate promptly. May be triggered by foreign bodies, infectious agents, or antigens that cause delayed hypersensitivity. Found in 3–10% of livers at autopsy (see also ➔ hepatic granulomas).

Intestinal granulomas most commonly associated with ➔ Crohn's disease and ➔ lymphoma. ➔ Tuberculosis is important differential, in which often display caseous necrosis. Also seen in primary neutrophil immunodeficiencies (e.g. ➔ chronic granulomatous disease).

Gut hormone profile

See: ➢ 'Gut hormone profile', p. 148.

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[5] Wong NA *et al.* (2014). *Curr Opin Support Palliat Care* **8**: 170–9.

[6] Kambham N *et al.* (2014). *Adv Anat Pathol* **21**: 301–20.

Section 4

H

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Haemangioma

Epidemiology and pathogenesis

Vascular lesion, and most common benign liver neoplasm. Prevalence 1–20% with ♀:♂ ratio 5:1 (may be higher in pregnancy). Usually identified at age 30–50y. Can occur as part of other syndromes (e.g. ➲ hereditary haemorrhagic telangiectasia, von Hippel–Lindau).

Clinical features

Most lesions <5cm (rarely >20cm), and asymptomatic. Very rarely painful, unless very large, or haemorrhage/rupture.

Investigation

- US demonstrates solitary uniform echogenic mass with well-demarcated border.
- CT shows low-density lesion with delayed contrast filling.
- Hyperintense on T2-weighted MRI.

Management

- Usually no treatment or follow-up required.
- Surgery indicated if haemangioma very large and symptomatic, increasing in size (e.g. on 6–12 monthly US), or diagnosis uncertain (misdiagnosis of malignant liver tumour as haemangioma well recognized).

Haemobilia

- Bleeding into biliary tree is an unusual cause of ▲ **acute upper GI tract bleeding** ▲. Causes include blunt or penetrating trauma, instrumentation (e.g. liver biopsy, ERCP, ➲ TIPSS), ➲ gallstones, hepatic artery aneurysms, bile duct (‘choledochal’) varices, ➲ liver abscesses, and tumours (e.g. ➲ hepatocellular carcinoma).
- May be associated with RUQ discomfort and jaundice (due to intraluminal blood clot or underlying disease, such as tumour).
- Making diagnosis often requires consideration of possibility (e.g. in patients with ↓ BP and Hb post-liver biopsy). At endoscopy, finding blood in the second part of the duodenum without a clear bleeding point should be followed by close inspection of ampulla with duodenoscope and ERCP if any risk factors present for haemobilia. Source of bleeding may be suggested on CT, and bleeding point defined by angiography.
- Management involves correcting coagulopathy and biliary decompression with endoscopic stent if obstructed. Usually settles spontaneously, but may require angiographic embolization, and rarely surgery. Fully covered metallic biliary stents may be helpful in tamponading bleeding point in extrahepatic bile duct.

Haemochromatosis

Epidemiology and pathogenesis

- Iron overload is associated with a variety of genetic and acquired conditions, of which *HFE* haemochromatosis is the most common. Normal total body iron is 3–4g, but in haemochromatosis may be >20g. Other causes of secondary iron overload include repeated blood transfusions and excess dietary iron.
- 90% of cases due to substitution of tyrosine for cysteine at position 282 of *HFE* gene on chromosome 6 (C282Y mutation). Autosomal recessive inheritance, with 10% of northern European populations heterozygous (and 1% homozygous) for C282Y; highest incidence in Ireland. Low penetrance of clinical disease, partly due to menstruating iron loss in pre-menopausal women.
- H63D^{++} (an alternative *HFE* mutation) homozygosity or C282Y^{+-}/ H63D^{+-} compound heterozygous genotypes may have ↑ ferritin ± transferrin saturations but rarely develop clinical iron overload.
- Understanding of mechanism of iron overload is incomplete, but may involve ↓ expression of HFE gene product at cell surface, and ↑ affinity of transferrin receptor for transferrin. Mutations in gene encoding transferrin receptor 2 (TfR2) associated with a small number of cases. In addition, ➲ hepcidin levels low and ∴ iron continues to be absorbed from duodenum.
- Relationship between alcohol and iron overload is complex. In patients with haemochromatosis, cirrhosis 9× more common in those drinking >60g alcohol/d. Reasons unclear, but probably due to co-factor effect of alcohol and iron overload on oxidative stress, hepatic stellate cell activation, and hepatic fibrogenesis. Hepatic iron overload may also occur in ➲ alcoholic liver disease *per se*, independent of haemochromatosis, but C282Y mutation should be excluded in alcoholic patients with any evidence of iron overload.
- C282Y heterozygosity has been linked to a number of other clinical scenarios, including ➲ porphyria cutanea tarda, ↑ fibrosis in ➲ hepatitis C, ➲ alcoholic liver disease, and non-alcoholic steatohepatitis (see ➲ non-alcoholic fatty liver disease).

Clinical features

- *Abdominal*: hepatomegaly, cirrhosis, ➲ hepatocellular carcinoma (15% of untreated cases), splenomegaly.
- *Cardiac*: cardiomyopathy (most commonly dilated, but occasionally restrictive), dysrhythmias.
- *Endocrine*: diabetes mellitus, hypogonadotropic hypogonadism (amenorrhoea or impotence), fatigue, panhypopituitarism, testicular atrophy, thyroid dysfunction.
- *Skin*: pigmentation ('bronze diabetes'), ➲ porphyria cutanea tarda (vesicular rash, back of hands), loss of axillary/pubic hair (secondary to hypopituitarism).
- *Skeletal*: chondrocalcinosis and pseudogout (often affecting knees), arthritis in 2nd and 3rd metacarpophalangeal joints, arthralgia.

Investigations

- LFTs. Often normal or minimally deranged.
- Fasting glucose and HbA1c.
- Serum ferritin. Upper limit of normal: ♂=300μg/L, ♀=200μg/L. In absence of other causes of elevated ferritin (e.g. acute phase reaction/chronic inflammatory diseases), serum ferritin >1,000μg/L strongly suggests haemochromatosis.
- Transferrin saturation. >45% suggestive of iron overload.
- *HFE* gene testing. C282Y gene analysis useful, but incomplete penetrance of homozygous mutations and fact that haemochromatosis also occurs in wild-type patients necessitate full biochemical tests in those with features suggestive of iron overload.
- MRI highly specific (80–100%) and sensitive (84–91%) for liver iron overload. Consider cardiac MRI in those with dysrhythmias.
- Liver biopsy. Less commonly required but remains gold standard for diagnosis of iron overload, with assessment of severity and pattern of Perl's haemosiderin stain (grade I–IV siderosis), and measurement of hepatic iron index (HII; μmol iron/gram dry weight of liver/age in years). HII >1.9 suggests hereditary haemochromatosis. Biopsy not needed for diagnosis if ferritin >1,000μg/L and C282Y homozygous.
- LH/FSH. May be ↓, with impaired response to gonadotrophin-releasing hormone.

Management

Aim is to ↓ serum iron levels.

- Venesection. Initially weekly. Remove 1 unit blood (450ml; 0.25g iron), with measurement of ferritin and Hb every 4–6 sections. Aim for Hb at lower end of normal range, and ferritin 50–100μg/L. May take 2y, but when achieved can ↓ venesection rate to 3–6 monthly. Patients may become blood donors to achieve target ferritin levels.
- Iron chelation. Desferrioxamine infusion 2g three times weekly occasionally needed when venesection not tolerated (e.g. patients with heart failure). Less effective, and rarely 1st line treatment.
- Exclude ➤ hepatocellular carcinoma, especially if cirrhotic, with 6-monthly > αFP + US.
- Management of diabetes follows standard protocols. Refer to endocrinologist for management of hypogonadotropic hypogonadism. Hormone replacement often required.
- Treatment of arthralgia with simple analgesia ± anti-inflammatories. Typically poor response to venesection.
- Strongly advise stopping/minimizing alcohol (no safe lower limit).
- Screening of relatives for haemochromatosis vital for siblings. If index case C282Y$^{+/+}$, screen using genetic analysis, transferrin saturation, and serum ferritin. If index case does not have genetic mutation identified, screen biochemically. For children of affected parents, consider testing when reach age of consent. Normal life span expected in patients who commence treatment before onset of diabetic or liver complications.
- Liver transplantation can be performed for end-stage liver disease.

Guideline

EASL clinical practice guidelines for *HFE* haemochromatosis (2010).

Haemolytic–uraemic syndrome (HUS)

Aetiology

Acquired and inherited forms. Particular interest for gastroenterologists is association (in 90%) with Shiga toxin-producing ➲ *E. coli*.

- *E. coli* 0157:H7 has caused several outbreaks globally. Organism not commensal human gut flora, but present in 1% of healthy cattle. Commonly acquired from unpasteurized milk or uncooked meat, but only 5% of infections lead to HUS.
- Major outbreak in Europe in 2011 caused by enteroaggregative *E. coli* O104:H4. Traced back to fenugreek sprouts grown from contaminated seeds imported from Egypt, though these results debated.
- Other associated enteric pathogens include ➲ *Shigella*, ➲ *Salmonella*, ➲ *Yersinia*, and ➲ *Campylobacter*.

Clinical features

- Characterized by microangiopathic haemolytic anaemia (MAHA), consumptive thrombocytopaenia and renal failure.
- Initial presentation with acute abdominal cramps, bloody diarrhoea, nausea, and vomiting. Incubation 2–5d. >90% resolve with no long-term sequelae.
- Bruising/bleeding, renal failure, and central nervous system (CNS) involvement (≈20%; seizures, encephalopathy) develop ≈1wk later. Hypertension in 25%.
- Children <5y and elderly most susceptible.

Investigation

- FBC will show ↓ Hb and ↓ plt.
- Microangiopathic haemolysis confirmed by ↑ Bn, ↓ haptoglobin, and presence of schistocytes on blood film.
- Renal profile to quantify acute kidney injury and check electrolytes.
- Clotting screen should be normal in HUS.
- Stool cultures may grow causative organism.

Management

- Treatment of acute diarrhoeal illness predominantly supportive. Use of antibiotics and antidiarrhoeal agents linked to ↑ risk of HUS.[1]
- Early detection critical, and early and vigorous volume expansion ↓ risk of severe kidney injury. Monitor UO; refer early to renal unit/ITU if oliguric.
- Red cell transfusion as indicated by magnitude and trend of ↓ Hb, alongside degree of haemodynamic compromise and symptoms.
- If severe thrombocytopaenia or active bleeding, discuss use of platelet transfusions with haematologist. Thrombocytopaenia develops due to aggregation of platelets into thrombi in microcirculation. Platelet transfusions ∴ have potential to exacerbate, so careful risk-benefit assessment required.
- General role of eculizumab (complement inhibitor) and plasma exchange not established.
- Approximately 80% of patients recover completely; 5% require long-term renal replacement therapy, and 5–10% die. Those who develop chronic kidney disease require follow-up in low clearance renal clinic.

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[1] Rahal EA et al. (2012). *Front Cell Infect Microbiol* **2**: 1–7.

Haemorrhoids

- Dilated vascular channels located in left lateral, right posterior, and right anterior positions within anal canal. Normal part of human anatomy, but can lead to prolapse, bleeding, and itching. Symptomatic haemorrhoids in 10–30% of adult population, with additional asymptomatic cases identified incidentally at colonoscopy (up to 40%). External haemorrhoids covered with squamous epithelium; internal haemorrhoids classified into four groups (Box 4.26).
- Exact pathogenesis not clear, but may be due to failure of supporting structures. Upright posture and prolonged time straining at stool do not help. Pregnancy also precipitating factor.

Box 4.26 Classification of internal haemorrhoids

Grade 1 Bleeding with defaecation.
Grade 2 Prolapse with defaecation but return naturally to their normal position.
Grade 3 Prolapse at any time, especially with defaecation, and can be replaced manually.
Grade 4 Permanently prolapsed.

Treatment

Based on grade. Grades 1 and 2 usually respond to diet: ↑ fibre and fluid intake to ensure soft stool which is easy to pass. Over-the-counter preparations often contain lubricants, astringents, vasoconstrictors, and antiseptics. Important constituents in prescribed preparations are steroids and local anaesthetics to reduce inflammation and provide relief from painful defaecation. Do not use topical steroids for more than few days and beware of possibility of perianal candidiasis, which should be treated with topical nystatin.

If these fail and patient does not have grade 4 haemorrhoids (which usually need surgical haemorrhoidectomy), aggressive non-surgical treatments include sclerosing agents, band ligation, cryotherapy, electrocoagulation, and use of heater probe (only first two in common use).

- Sclerosing agents. Aim is to inject irritant (e.g. arachis oil containing 5% phenol) into submucosa above haemorrhoid to create fibrosis and prevent prolapse. Pelvic sepsis rare, but usually occurs 3–5d post-procedure, and can be life-threatening. Recurrence up to 30%.
- Band ligation. Widely used for 2nd and 3rd degree haemorrhoids. Stop antiplatelets and NSAIDs for 5d before and after treatment. Immediate pain signifies placement too close to dentate line; the band needs to be removed. Complications include bleeding (usually controlled by tamponade with Foley catheter balloon, but sometimes needs adrenaline injection or even small suture), and sepsis.
- External haemorrhoids visible and palpable on wiping, but cause few symptoms apart from slight interference with personal hygiene. However, may thrombose, causing rapid appearance of lump and pain. Usually subside after few days.

Heavy chain disease

Rare neoplastic disorders of B cells with abnormal truncated monoclonal heavy chains.[2] Form of paraproteinaemia. Four subtypes, depending on immunoglobulin involved. Least uncommon: ➲ α-chain disease (IgA), usually found in Mediterranean regions. Infiltration of small intestine produces abdominal pain, masses, weight loss, malabsorption, steatorrhoea, and hypocalcaemia, with complications including obstruction, intussusception, and perforation. Diagnosis by small bowel biopsy. Disease confined to mucosa usually indolent and may be treated with antibiotics.

γ-chain disease (IgG) presents with fever, night sweats, weight loss, lymphadenopathy. May develop hepatosplenomegaly.

Helicobacter pylori (HP)

- Slow-growing micro-aerophilic Gram-negative spiral rod, causally linked with ➲ gastritis, ➲ peptic ulceration, ➲ gastric cancer (adenocarcinoma), and ➲ gastric lymphoma. Usually acquired in childhood. Prevalence varies with age, country, and social class. Transmission person-to-person.
- Acute infection can occur, causing neutrophilic gastritis that can lead to epigastric discomfort with nausea and vomiting.
- Infection in adults usually chronic, producing non-atrophic superficial gastritis. Physiological effect of this process on acid and gastrin secretion depends in part on area of stomach affected. Gastritis in body of the stomach tends to ↓ acid output (although there is rebound hypergastrinaemia), while antral-predominant gastritis is associated with ↑ acid output and duodenal ulceration.
- Progression to atrophic gastritis may occur and may explain in part association with gastric cancer.

Testing for *Helicobacter pylori*

Available methods for testing

Tests not requiring mucosal biopsy

Include urea breath tests, stool antigen tests and serology (see Table 4.16). Tests on saliva, buccal scrapes, or urine are unreliable at present. Serum tests useful for confirming infection but unreliable for confirming eradication, as antibody titres do not always fall.

- Breath tests use urea labelled with ^{13}C or ^{14}C. More commonly used ^{13}C method requires mass spectrometer for analysis involving delay of, at best, several days. Test requires patient to be off proton pump inhibitors (PPI) therapy for 14d and H_2 antagonists for 3d, and for at least 14d to have elapsed since eradication therapy. Most validated method of demonstrating HP infection, and accurate at determining ongoing infection.
- Stool antigen testing shows comparable sensitivity (94%) and specificity (98%) for diagnosis to urea breath testing, but may need to be delayed for 3mo after therapy to confirm eradication. Patient preparation similar to that for urea breath test.

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[2] Bianchi G *et al.* (2014). *Oncology (Williston Park)* **29**: 45–53.

- Serology testing now relegated to 3rd line as performance varies between laboratories (so local validation essential). Remains positive for long time after successful treatment, so not useful for demonstrating eradication.

Tests requiring mucosal biopsy

- Campylobacter-like organism (CLO) test is a rapid diagnostic, based on ability of HP to secrete urease and convert urea to ammonia and CO_2. Performed during upper GI endoscopy, where biopsy of antral mucosa is placed into urea-containing medium; colour indicator changes from yellow to red in the presence of HP. Sensitivity and specificity comparable to urea breath test, but may be falsely negative in patient taking PPI.
- Otherwise, biopsy generally unnecessary unless culture and antibiotic sensitivities required. These may also help confirm diagnosis in patient started on PPI for acute upper GI bleed, in whom non-invasive and CLO test may be falsely negative. Routine H&E histology will show HP if large numbers present: special (e.g. silver) stains more sensitive for smaller loads.

Treatment

- Cure requires combinations of at least 2 antibiotics and non-antibiotics such as → PROTON PUMP INHIBITORS (PPI). Antibiotic resistance is the major reason for HP treatment failure. Pretreatment sensitivity testing not routinely performed, so the proportion of failed treatments due to resistant organisms is not known.
- The standard therapeutic strategy has been to use triple therapy 1st line, consisting of a PPI with 2 antibiotics for 7d (Box 4.27). Clarithromycin is the single most effective antibiotic and d in eradication rates of 70% are seen if resistance is present. Typically used 1st line with amoxicillin. In areas with high clarithromycin resistance, substitute with metronidazole to be used alongside amoxicillin.
- Because of increasing resistance to clarithromycin and metronidazole, recent guidelines now recommend a quadruple regimen (bismuth or non-bismuth) 1st-line. Tailored therapy based on antimicrobial susceptibility test results is ideal if available.
- Failure of eradication can be dealt with by:
  - Changing antibiotics. Fluoroquinolones (levofloxacin important salvage therapy, but resistance rates already ~15%), rifabutin, and tetracyclines (contraindicated in children) often effective.
  - Adding 4th agent (if treated with triple therapy). Usually bismuth subcitrate (De-Nol®) or subsalicylate (Pepto-Bismol™).
  - Extending duration of treatment to 10–14d.
- After failure of 2nd line therapy, salvage regimens should be based on susceptibility testing, if available. Local prevalence of sensitivities should be considered when prescribing treatment.

Table 4.16 Accuracy of diagnostic tests for *Helicobacter pylori*

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Urea breath test	90	96	98	84
Stool antigen	96	83	98	96
Serum IgG	91	97	95	85
CLO test	90	100	100	84
Histology	89	78	93	85

PPV, positive predictive value; NPV, negative predictive value.

Box 4.27 Recommended regimens to treat *H. pylori*

PPI triple therapy

PPI bd + amoxicillin 1g bd + clarithromycin 500mg bd or metronidazole 500mg bd.

Quadruple therapy

PPI bd + bismuth 2 tabs bd + metronidazole 500mg bd + tetracycline 250–500qds.

Follow-up after eradication

- Routine follow-up testing not performed. However, failed therapy in an ulcer patient is very often associated with ulcer recurrence. Certainly in patients with complicated peptic ulcer disease (i.e. bleeding or perforation), documentation of eradication is advised before maintenance antisecretory therapy is stopped.
- Confirmation of eradication usually performed with urea breath test 4–6wk after completing course of therapy. Stool antigen testing can be used as alternative, but not serology as recognizes past infection.
- After failure of eradication, if an endoscopy if considered, antimicrobial susceptibility testing should be completed to tailor treatment.
- Reinfection rates with HP are very low.

Guideline

European Helicobacter and Microbiota Study Group consensus report on management of *Helicobacter pylori* infection (2017).

HELLP syndrome

Background

HELLP syndrome (**H**aemolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets) is a thrombotic microangiopathy that occurs in 6/1,000 pregnancies. Part of spectrum of severe hypertensive disease of pregnancy that includes pre-eclampsia, and arises in 5–10% of ♀ with the latter. Risk factors include maternal age, multiparity, and white ethnicity.

Clinical features

- Presentation usually Wk 27–36 of pregnancy, but after delivery in 30%.
- May be asymptomatic but classic features include malaise, RUQ pain, nausea, vomiting, and symptoms/signs of pre-eclampsia (thirst, headache, blurred vision, proteinuria, and hypertension). Clinical jaundice in 5%.
- Maternal complications include DIC (20%), placental abruption, and subcapsular haematoma.
- Maternal mortality 1%; perinatal mortality up to 30%.

Investigations

See also ► Approach to liver problems in pregnancy.

- FBC and blood film confirm microangiopathic haemolytic anaemia (MAHA). Hb usually <90g/L with schistocytes. Platelets typically <100×10^9/L. LDH >600IU/L and ↓ haptoglobin suggest haemolysis.
- AST/ALT levels usually 2–15× ULN (mean ~250U/L), and Bn 2× ULN (i.e. ~40μmol/L). Massive ↑ AST/ALT (e.g. >1,000U/L) suggests liver infarction. INR normal unless DIC or severe liver injury.
- Renal failure in up to 8%.
- Liver biopsy high risk and rarely required. When performed, microscopic features similar to pre-eclampsia.
- US or CT may demonstrate subcapsular haematoma or infarction.

Management

- Delivery as soon as possible (ideally beyond Wk 32 by vaginal delivery) usually leads to prompt resolution. Steroids often given prior to delivery (largely for speeding foetal lung maturity), but no clear evidence these improve outcomes of HELLP.
- Hypertension should be treated with labetalol, hydralazine, or nifedipine. Avoid diuretics due to uteroplacental hypoperfusion.
- IV magnesium if seizures.
- ➜ Liver transplantation has been successful in acute liver failure.
- Recurrence of HELLP in future pregnancies <5%.

Helminth infection

Parasitic worms (helminths) classified into ➜ roundworms (nematodes), ➜ tapeworms (cestodes), and ➜ flukes or flatworms (trematodes). Travel, migration, and exotic cuisine allow helminths to appear in any locale. They are complex and often well adapted to their host—so much so that light infection may cause no symptoms, with only heavy infestation resulting in disease. Almost never cause diarrhoea but potent cause of ➜ eosinophilia. Induce Th2 response (Il-4 mediated); this may limit multiplication but also inhibits excessive Th1 responses. Diseases characterized by Th1 responses (such as ➜ Crohn's disease and multiple sclerosis) are rare where helminths are common ∴ possible parasitic infection offers some protection.

Henoch–Schönlein purpura (Plate 46)

Epidemiology and pathogenesis

Henoch was a 19th-century German paediatrician. His eponymous syndrome should really be called Schönlein–Henoch, as first described by his teacher, Schönlein. Commoner in children (10–20/100,000/y), but can occur in adults. Small vessel vasculitis, associated with deposition of abnormally glycosylated IgA immune complexes in tissues.

Clinical features

- Clinical syndrome of palpable non-thrombocytopenic purpura, arthritis/arthralgia, and glomerulonephritis (IgA nephropathy), together with diffuse abdominal pain.
- Typically preceded by headache, anorexia, and fever.
- GI symptoms include pain, nausea, and vomiting. GI bleeding (can originate from small or large intestine) in 40%. Less common complications include ➲ intramural haematomas, ➲ intussusception, ➲ cholecystitis, ➲ appendicitis, bowel infarction, and peritonitis.

Investigation

- Diagnosis principally clinical, but supported by biopsy showing predominant IgA deposition in any tissue (but in particular skin, kidney, or GI tract).
- Bloods:
  - FBC may show ↓ Hb and ↑ WBC.
  - ESR/CRP normal or ↑.
  - Renal function abnormal if glomerulonephritis.
  - Serum IgA may be raised, but can be normal.
- Urine. Positive for blood and protein if glomerular lesion.
- Imaging. US or CT abdomen if intussusception or perforation suspected. Kidneys appear echobright on US if glomerulonephritis.

Management

- In most cases, only symptomatic management required, with analgesia/anti-inflammatories ± bed rest for those with severe arthralgia/abdominal pain.
- Steroids may be used in severe cases.
- Management of ▲ **acute upper gastrointestinal bleeding** ▲, ▲ **acute lower gastrointestinal bleeding** ▲, and ➲ intussusception follow standard protocols.
- Severe GI vasculitis has been successfully treated with IVIg, IV methylprednisolone, or plasma exchange.[3]
- If severe renal involvement, request a nephrology consult regarding need to biopsy and use of immunosuppression.

Prognosis

Natural history is usually of complete resolution, typically within 8wk. May recur in ⅓, and in particular can lead to chronic kidney disease.

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[3] McCarthy HJ & Tizard EJ (2010). *Eur J Pediatr* **169**: 643–50.

Hepatic drug metabolism

Most drugs are lipophilic, hence difficult to eliminate from body. Hepatic metabolism to more polar, inactive compounds that are water-soluble enhances urinary excretion. Three phases are recognized:

- Phase 1 reactions.
    - Account for most clinically important drug interactions.
    - Drugs undergo reduction or oxidation, with insertion of a hydroxyl group, catalysed by cytochrome P450 (CYP) superfamily of enzymes within endoplasmic reticulum. 57 human CYP isoforms identified to date, of which CYP1, CYP2 (especially CYP2D6), CYP3, and CYP3A4 play dominant roles.
    - Inhibition or induction of these enzymes underlie many clinically important drug interactions (Table 4.17), and some manifestations of ➲ drug-induced liver injury. **Inhibition** typically rapid as competitive process; **induction** slower as requires new enzyme synthesis. In most cases, CYP450 inactivates drugs and hence inhibition will enhance, and induction diminish, potency and toxicity. However, occasionally CYP450 will be responsible for activating pro-drugs (e.g. clopidogrel) or generating toxic metabolites (e.g. NAPQI from paracetamol), in which case inhibition and induction have the opposite clinical effects.
- Phase 2 reactions.
    - Drugs conjugated within hepatocyte cytoplasm to polar ligands, enhancing water solubility.
    - Major reactions include glucuronidation (paracetamol, opioids, benzodiazepines, tricyclic antidepressants, antipsychotics, NSAIDs), sulphation (paracetamol, steroids, methyldopa), and acetylation (sulfonamides, isoniazid, dapsone). These can be subject to competitive inhibition by other substrates, although few examples of proven clinical relevance (one exception is ↓ clearance of lorazepam by valproic acid, resulting in excess sedation).
- Phase 3 reactions.
    - Drugs transported into bile by ATP-dependent transporters. Two principal superfamilies: ATP-binding cassette (ABC) and solute-linked carriers (SLC) transporters.
    - Importance of drug–drug interactions at this level only recently appreciated (Table 4.18).

Table 4.17 Common CYP450 inhibitors and inducers

CYP450 Inhibitors	CYP450 Inducers
Macrolide antibiotics	Carbamazepine
Cimetidine	Phenytoin
Ciprofloxacin	Phenobarbital
Antifungal azoles	Rifampicin
Sulfonamides	Alcohol (chronically)
Isoniazid	Cigarette smoking
Sodium valproate	St John's wort
Verapamil	
Alcohol (acutely)	
Grapefruit juice	

! Pitfalls. Drugs frequently involved in clinically significant Phase 1 drug–drug interactions.

CYP450 inhibitors ↑ risk of toxicity, inducers lead to loss of efficacy.

- Warfarin.
- Ciclosporin.
- Theophyllines.
- Statins.
- Antiretroviral protease inhibitors.
- Oral contraceptive pill.

Box 4.28 Clinically significant Phase 3 drug–drug interactions.

Substrates

- Digoxin.
- Vinblastine, vincristine.
- Adefovir, indinavir.
- Anthracyclines.
- Methotrexate.
- Penicillins.
- Etoposide.
- Pravastatin.
- 6-MP.
- Ciclosporin, tacrolimus.

Inhibitors of transporter (↑ risk of toxicity)

- Ciclosporin (also substrate).
- Macrolides.
- Ketoconazole.
- Amiodarone.
- Quinidine.
- Verapamil.
- Rifampin (inhibits some transporters, induces others).
- Indometacin.
- Furosemide.
- Sildenafil.
- Ritonavir.
- Saquinavir.
- Tamoxifen.

Inducers of transporter (↓ efficacy)

- Rifampicin (inhibits some transporters, induces others).
- St John's wort.
- Chlorambucil.
- Carbamazepine.

Hepatic granulomas

- Found in 2–10% of liver biopsies. Range of causes, although autoimmune liver disease, ➔ sarcoidosis, and ➔ TB account for most (Box 4.29). Frequently found in patients with ➔ HIV, often related to underlying infection (*M. tuberculosis*, *M. avium intracellulare*, cytomegalovirus, *Toxoplasma*), or lymphomatous infiltration. May develop as part of lupus-like drug reaction.
- Granulomas can be non-caseating (e.g. in sarcoidosis) or caseating (characterized by central necrosis; seen in TB).
- Presentation varied (reflecting wide range of causes). Hepatomegaly in 20%. Granulomatous hepatitis presents with 'pyrexia of unknown origin' in 50%, and debate as to whether variant of sarcoidosis.
- LFTs often show ↑ ALP/γGT. Range of diagnostic tests may be needed to identify cause (e.g. CXR and serum angiotensin-converting enzyme (ACE) for sarcoidosis).

- Liver biopsy required to establish diagnosis.
- Treatment depends on cause. Corticosteroids may improve fever and LFTs in hepatic sarcoid/idiopathic granulomatous hepatitis. Drug-related granulomatous reaction usually responds to cessation.

Hepatic steatosis

- Spectrum, characterized by fat deposition within hepatocytes. Can be microvesicular or macrovesicular. Ranges from fatty liver alone (steatosis) to fatty liver with inflammation (steatohepatitis).
- Affects >20% of US adult population, with most common associations including alcohol, obesity, and diabetes mellitus.
- May occur with use of alcohol (see ➔ alcoholic liver disease) or in its absence (➔ non-alcoholic fatty liver disease (NAFLD)). Non-alcoholic steatohepatitis (NASH) considered part of spectrum of NAFLD, but associated hepatocyte inflammation and cell death in NASH may lead to fibrosis and cirrhosis. Prognostic factors in developing fibrosis include age >45y, diabetes mellitus, and high ➔ body mass index (BMI).
- Other causes of hepatic steatosis include ➔ abetalipoproteinaemia, ➔ acute fatty liver of pregnancy (classically microsteatosis), ➔ HELLP syndrome, inborn errors of metabolism, ➔ parenteral nutrition, ➔ Wilson's disease, and medications (amiodarone, methotrexate, sodium valproate, highly active antiretroviral therapy (HAART)).
- Most patients are asymptomatic. Hepatomegaly common, but splenomegaly and ascites suggest cirrhosis.
- In liver function tests, AST/ALT ratio >2 suggests alcohol use, whereas ratio <1 is more consistent with NAFLD.
- On US, liver hyperechogenic or bright. Steatosis detected only when >30% fatty change present.
- Management depends on underlying cause (e.g. weight reduction, diabetic control, abstinence from alcohol, drug cessation). Steatosis may completely resolve, with no residual architectural damage.

Box 4.29 Causes of hepatic granulomas

Drugs

- Allopurinol.
- Sulfonamides.
- Hydralazine.
- Procainamide.
- Gold.
- Phenytoin.
- Isoniazid.
- Carbamazepine.
- Chlorpropamide.
- Phenylbutazone.
- Quinidine.
- Tolbutamide.

Infection

- ➔ *Mycobacterium tuberculosis*.
- *M. avium intracellulare*.
- *Brucella*.
- Syphilis.
- Leprosy.
- Toxoplasmosis.
- ➔ Schistosomiasis.
- ➔ Whipple's disease.
- *Coxiella burnetii*.
- ➔ HIV.
- ➔ Hepatitis A/B/C.

Immunological disease

- ➔ Crohn's disease.
- ➔ Sarcoidosis.
- ➔ Systemic lupus erythematosus.
- Idiopathic granulomatous hepatitis.
- ➔ Primary biliary cholangitis (PBC).
- ➔ Autoimmune hepatitis.
- ➔ Overlap syndromes.
- ➔ Polyarteritis nodosum.
- Wegener's granulomatosis.

Neoplasia

- Hodgkin's lymphoma.
- Non-Hodgkin's lymphoma.
- Renal cell carcinoma.

Industrial

- Berylliosis.

Other

- Idiopathic.

Hepatitis A

Epidemiology

RNA virus, and cause of 50% of reported cases of acute viral hepatitis in UK. Transmission faecal–oral via infected water or ingestion of uncooked contaminated shellfish or foods. Most common vaccine-preventable infection in travellers to areas of high endemicity (e.g. N Africa, S America, where >95% of children exposed by age 10).

Clinical features

- HAV only causes acute (never chronic) hepatitis.
- Risk of developing jaundice ↑ with age (79% in patients >15y).
- Incubation period 2–6wk, with jaundice, nausea, fever, and fatigue. Some patients remain asymptomatic.
- Prolonged cholestasis may occur in 5%. ▲ **Acute liver failure** ▲ reported in <0.1% of cases, but may be more common in conjunction with chronic ➲ hepatitis C.

Investigation

LFTs demonstrate markedly ↑ ALT (often >1,000U/L) during acute icteric phase. Diagnosis confirmed by HAV IgM in serum, which appears 5–8wk after symptom onset. Liver biopsy rarely indicated.

Management

- No specific treatment necessary (i.e. supportive).
- See ▲ **acute liver failure** ▲ for very rare severe hepatitis A.
- 'Prevention is better than cure': HAV vaccine very effective, and should be offered to: travellers to areas of increased risk, IV drug users, men who have sex with men, patients with haemophilia or chronic liver disease (including ➲ hepatitis C, who may have increased risk of acute liver failure), and those at occupational risk (e.g. childcare centre workers). 1ml of vaccine given initially, and then at 6–12mo, provides 95% protection for >20y.

Hepatitis B

Epidemiology

- More than 300 million people worldwide are infected with hepatitis B DNA virus (HBV), with chronic infection in 0.1–2% in Western Europe and USA, and up to 20% in areas of SE Asia.
- Most common route of transmission is perinatal (90% infection rate in infants born to HBeAg-positive mothers), but blood inoculation through unclean needles remains important. Sexual transmission accounts for 30% of infections in developed countries. Not transmitted by breastfeeding.

Clinical features

Acute hepatitis B

Jaundice, malaise, and RUQ pain may develop 1–4mo after infection. Although ▲ **acute liver failure** ▲ occurs in 2%, acute hepatitis leads to viral clearance in >95% of infected adults.

Chronic hepatitis B

Defined by HBsAg positivity in serum for >6mo. Age at infection strongly determines chronicity, reflecting host immunity (>90% in neonates, 20–50% age 1–5y, <5% in adults). Different patterns of chronic infection correlate with serological markers (Table 4.18). Highest rate of complications in highly replicating disease, i.e. HBeAg$^+$ chronic hepatitis B (CHB), or HBeAg$^-$ CHB (previously called pre-core mutant). Spontaneous clearance (becoming HBsAg$^-$) in 1% of chronic infections/y.

Complications

- Cirrhosis. Once developed (usually 30–40y after perinatal infection, but very variable), 5y survival ≈80%. Falls to 35% after episode of decompensation (see ► Approach to cirrhosis and chronic liver disease).
- ➲ Hepatocellular carcinoma. Nearly 100× ↑ risk in chronic hepatitis B. Annual incidence 2–6% in those with cirrhosis, 0.4–0.6% in non-cirrhotics.
- Membranous glomerulonephritis.
- ➲ Polyarteritis nodosa.

Investigations

- HBV serology (see Table 4.18 and Box 4.30):
  - HBsAg indicates ongoing infection.
  - HBeAg presence confirms active high viral replication, but negative in eAg$^-$ CHB.
  - Anti-HBe reciprocal of HBeAg.
  - Anti-HBc IgM seen in acute infection, and anti-HBc IgG (in previous or ongoing chronic infection).
  - Anti-HBs indicates resolved infection or successful vaccination.
- HBV DNA by PCR. Essential if HBsAg$^+$ HBeAg$^-$ in order to exclude HBeAg$^-$ CHB (HBeAg$^-$, HBV DNA >2,000IU/ml, ↑ ALT).
- HBV genotypes. Genotypes A–D vary in treatment response.
- HDV and HIV serology should also be sent.
- Liver function tests: AST/ALT usually >1,000U/L in acute hepatitis. May fluctuate in chronic infection, but ALT <80U/L strongly predicts lack of HBeAg seroconversion (loss of HBeAg, development of serum anti-HBe) in response to antiviral therapy (i.e. lack of sustained treatment response).
- ➢ α-fetoprotein. Perform 6-monthly with liver US, especially in cirrhotics, in view of ➲ hepatocellular carcinoma risk.
- Transient elastography. Liver stiffness (LS) >11kPa is an indication for treatment; LS 6–10kPa requires liver biopsy as does LS<6kPa with abnormal ALT and HBV >2,000IU/ml; while LS <6kPa with normal ALT and HBV <2,000IU/ml can be surveyed annually.
- ➲ Liver biopsy. Rarely needed in acute hepatitis B, but may be indicated in chronic infection when treatment considered (see Fig. 4.11) or according to transient elastography findings.

Table 4.18 Patterns of HBV infection and serology

Clinical state	HBsAg	HBeAg	Anti-HBc IgM	Anti-HBc IgG	Anti-HBs	Anti-HBe	HBV DNA	Serum ALT	Comments
Acute infection	+	+ /–	+	+/–	–	+/–	+/–	↑↑	HBsAg may be –ve at presentation
HBeAg$^+$ CHB	+	+	–	+	–	–	+++	N/↑	ALT may be >1,000U/L, and anti-HBcIgM$^+$ in flare of disease
HBeAg$^-$ CHB	+	–	–	+	–	+	++	↑	Common in S Europe
Vaccinated	–	–	–	–	+	–	–	N	
Resolved infection	–	–	–	+/–	+	+/–	–	N	Anti-HBc IgM$^+$ if recently resolved

Box 4.30 Practice points in interpreting HBV serology

- HBsAg may rarely be negative at presentation in acute hepatitis B (and particularly in severe/fulminant disease, because of profound immune-mediated response and associated liver damage). However, anti-HBc IgM will be positive.
- HBeAg$^+$ confirms high level of HBV DNA (measurement of absolute level of virus rarely changes management in this setting). In contrast HBV DNA quantification essential in all cases where HBsAg$^+$, HBeAg$^-$.
- Anti-HBc IgM may occasionally be positive in acute flares of chronic infection. Differentiation from acute primary infection often difficult, but chronic infection may be suggested by knowledge of prior positive serology and subsequent lack of HBsAg seroconversion (as occurs in >95% of cases of acute infection). Liver biopsy may be needed to confirm chronic disease.

Management

Acute hepatitis B

No definitive evidence antiviral therapy affects disease course, but lamivudine, tenofovir, and entecavir have been given for fulminant HBV.

Chronic hepatitis B

- Usual goal of treatment is to suppress HBV replication, induce HBeAg seroconversion (clearance of HBeAg, appearance of anti-HBe), and ↓ liver injury. Ultimate goal is to clear HBsAg and prevent cirrhosis and HCC. European guidelines suggest that antiviral therapy should be considered in all patients with CHB with liver inflammation and HBV DNA >2,000IU/ml.
- ALT may be poor surrogate marker of inflammation/fibrosis (recent recommendations are that in context of CHB, ULN for ALT should be 30IU/ml for ♂ and 19IU/ml for ♀). Liver biopsy or non-invasive markers of fibrosis usually required.
- Immunotolerant CHB (i.e. HbeAg$^+$ CHB, high HBV DNA, normal ALT, with no suspicion of liver injury, or family history of cirrhosis or HCC) do not require immediate biopsy or treatment.
- Rate of HBeAg seroconversion with present antivirals closely related to pretreatment ALT (<10% if ALT <2× ULN, >50% if ALT >5× ULN). See → Section 5 for further information.
    - → PEGINTERFERON ALFA (IFN-α) induces HBeAg seroconversion in 30% at 1y, and HBsAg loss in 5–10%. Predictors of response: low pretreatment HBV DNA; high ALT (>3× ULN); high inflammatory score on biopsy; genotype A or B. Advantages include finite treatment course (48wk), no risk of resistance, and chance of HBsAg seroconversion. Disadvantages are subcutaneous administration, side effects (see ➲ hepatitis C), and contraindicated in decompensated cirrhosis. If PEG-IFN has not produced a 1 log drop in HBV DNA by 12wk, or level <2,000IU/ml at 24wk, most authorities would advise swapping to oral antivirals.
    - → LAMIVUDINE, like other oral nucleoside/nucleotide analogue agents, has few side effects, and is easy to take. HBeAg seroconversion in 25% after 1y of use and 56% after 3y. Major problem is treatment-resistant YMDD variants in >40% after 3y of use, and most guidelines now suggest avoiding as monotherapy.
    - → TENOFOVIR. Low rate of viral resistance, and high viral control, but avoid in severe renal disease. Indicated for monotherapy.
    - → ENTECAVIR. Equally potent at viral control as tenofovir, but higher risk of viral mutations, particularly if previous lamivudine resistance. Important role, like tenofovir, as 1st monotherapy.
- Duration of treatment depends on range of factors, but most authorities advise additional or changed treatment if HBV DNA still detectable at 24 or 48wk. If HBeAg seroconversion achieved, treatment should be prolonged for additional 6–12mo. Many patients will remain on long-term therapy to chronically suppress viral replication.
- Special circumstances:
    - Cirrhosis secondary to HBV. Treat with oral antiviral therapy irrespective of eAg status and HBV DNA titre.

- Pregnancy. Mothers with HBV DNA >10^6 IU/ml require treatment >28wk gestation with oral antiviral therapy.
- Patients undergoing antibody induction/chemotherapy. Prophylactic treatment recommended in HBsAg$^+$ patients for at least 6mo after chemotherapy.
- Patients with HIV/HBV co-infection. Indications for treating CHB same as for HBV monoinfection, although treatment often given earlier due to more aggressive disease. Regimens beyond scope here, but combination therapy vital to avoid development of viral escape mutants of HIV or HBV. Lamivudine and tenofovir active against both HBV and HIV.

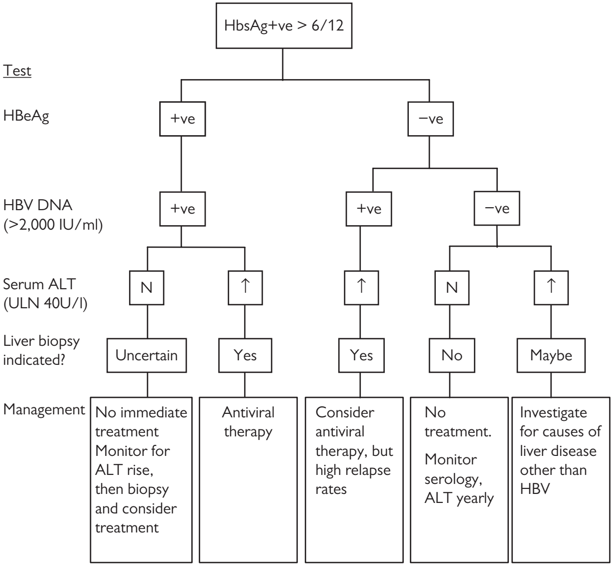
HbsAg+ve > 6/12
Test
HBeAg
+ve
−ve
HBV DNA (>2,000 IU/ml)
+ve
+ve
−ve
Serum ALT (ULN 40U/l)
N
↑
↑
N
↑
Liver biopsy indicated?
Uncertain
Yes
Yes
No
Maybe
Management
No immediate treatment Monitor for ALT rise, then biopsy and consider treatment
Antiviral therapy
Consider antiviral therapy, but high relapse rates
No treatment. Monitor serology, ALT yearly
Investigate for causes of liver disease other than HBV

Fig. 4.11 Management algorithm for chronic hepatitis B. *Note.* Surveillance for hepatocellular carcinoma in all chronically infected patients (e.g. 6-monthly αFP and US).

Vaccination

In UK, vaccination not universal, and there are recommendations for temporary passive immunization with hepatitis B immunoglobulin (HBIG) and active immunization (Table 4.19). HBIG contains high titre of anti-HBs, given at 0.1ml/kg after exposure (or birth to chronically infected mother). Active vaccination with 10 or 20μg HBsAg given at 0, 1, and 6mo.

Table 4.19 Indications for HBV immunization

Active (hepatitis B vaccine)	Passive (HBIG)
Family contacts of individual with HBV infection	Post-exposure prophylaxis
Babies born to infected mothers (± HBIG if mother $HBsAg^+$, $HBeAg^+$)	Newborns of mothers who are $HBsAg^+$, $HBeAg^+$ (with vaccine)
IV drug users	Newborns of mothers with acute hepatitis B in 3rd trimester
Regular receivers of blood (e.g. haemophilia)	
Patients with chronic renal failure	
Healthcare workers	
Sexual contacts of infected individual	
Travellers to high endemic areas	

Guidelines

🖱 EASL clinical practice guidelines for management of chronic hepatitis B (2012).

🖱 NICE guideline (CG165) for diagnosis and management of chronic hepatitis B (2012).

Hepatitis C

Epidemiology

- RNA flavivirus. Approximately 170 million people worldwide, and 250,000 in UK, infected with hepatitis C virus (HCV), and up to 2% of people exposed at some time (higher in Egypt, Asia, and Africa).
- Transmission mainly through injection drug use (>60% of cases in UK) or contaminated blood-product transfusion (virtually eliminated in developed countries with screening of donated blood). Use of non-disposable needles during treatment of ➔ schistosomiasis may have contributed to high prevalence in Egypt (15% of population). Skin piercing procedures of proven risk. Other high-risk individuals include: high-risk sexual behaviours, incarcerated persons, men who have sex with men, and HIV co-infection. Rate of HCV transmission in monogamous heterosexual relationships appears low (<6%). Transmission from mother to infant in ~5% of cases, but ↑ to 18% if mother co-infected with HIV. Breastfeeding transmission not reported. No risk factors reported in 10–20% of cases.
- Six main HCV genotypes, with subtypes (a–c). Geographical variation in predominant genotype (e.g. genotypes 1, 2, and 3 in Europe and USA; genotype 4 in Egypt and Middle East).

Clinical features

- Acute icteric hepatitis in <15% (although spontaneous viral clearance may then occur in up to 50%).
- Chronic infection in 50–85% of cases, defined by persistence of HCV RNA in serum. Usually clinically silent. Overall risk of progression to cirrhosis over 25–30y 5–25%, but may be lower (1–3%) in ♀ without co-factors (e.g. alcohol). Risk factors for disease progression include high circulating virus level, long duration of disease, ♂ sex, older age at acquisition, alcohol excess, steatosis, diabetes, and HIV/➲ hepatitis B co-infection.
- Up to 4% of patients/y with HCV cirrhosis develop ➲ hepatocellular carcinoma.
- Non-specific complaints common, including fatigue, headache, and poor concentration. HCV may have direct CNS effects.
- Extraintestinal manifestations have been associated with chronic HCV (Box 4.31), the pathogenesis of which remains uncertain.

Investigation

- Anti-HCV antibody. Confirms exposure, but not persistence of, infection. May be negative in early phase of acute infection.
- HCV RNA by PCR. Positivity confirms ongoing infection, with cut-off variable but usually 15IU/ml.
- HCV genotype. Essential to determine in patients considered for treatment, as influences regimen and response.

Box 4.31 Extrahepatic associations of hepatitis C

- Cryoglobulinaemia (detectable in 36–54% chronic patients):
  - Most asymptomatic.
  - Arthralgia and pruritus in 18%.
  - Neuropathy and glomerulonephritis in 2%.
- Mesangiocapillary/membranous glomerulonephritis.
- Sjögren's syndrome.
- Lichen planus.
- ➲ Autoimmune hepatitis.
- Thyroiditis.
- ➲ Polyarteritis nodosa.
- Polymyositis.
- ➲ Porphyria cutanea tarda.

- LFTs. ALT/AST ↑ ≈1.5–2.5× ULN in chronic HCV, but fluctuations throughout course of disease common. Poor correlation between level of ALT and either level of viraemia or severity of histological disease. Other liver disease may also need to be excluded.
- Liver biopsy determines degree of inflammation (grade) and fibrosis (stage), and may guide decision concerning need for treatment. Non-invasive markers of liver fibrosis (e.g. Fibrotest, Enhance Liver Fibrosis (ELF), or Fibroscan) increasingly used as alternatives.

- Additional blood tests:
    - Antismooth muscle antibodies because, although may be epiphenomenonal in chronic HCV, true ➲ autoimmune hepatitis is an association that can be exacerbated by antiviral therapy.
    - Thyroid function tests and antithyroid autoantibodies (as abnormalities more common in hepatitis C, and thyroid abnormalities may occur with interferon therapy, particularly in presence of antithyroid antibodies).
    - HBsAg should be tested as chronic ➲ hepatitis B associated with more progressive histological disease in those with HCV.
    - HIV testing in view of shared modes of acquisition.
- Abdominal US prior to liver biopsy, and to identify features of cirrhosis and ➲ portal hypertension. Repeat 6 monthly (with ▷ α-fetoprotein) in patients with proven cirrhosis, in view of risk of ➲ hepatocellular carcinoma.

Management

- Crucial to ensure patient aware of natural history of disease, as many believe progression to end-stage liver disease is inevitable and treatment ineffective. Progression usually seen in those who drink excess alcohol—no safe lower limit known.
- Patients should be advised not to donate blood, and risks of needle sharing by drug users should be reiterated. Avoid sharing razors and toothbrushes. Sexual transmission unusual, but condoms should be used during casual sexual contacts to lower risk of transmitting other infections (e.g. HIV). Prudent to test regular sexual partners of patients, but advise risk of transmission low.
- Vaccinate against ➲ hepatitis A and ➲ B, as co-infection may lead to disease progression (hepatitis B) or ▲ **acute liver failure** ▲.

Antiviral therapies

- Increased emphasis on individualizing treatment, but usual indications include positive anti-HCV antibody, positive HCV RNA, ↑ AST/ALT, and moderate to severe hepatitis or well-compensated cirrhosis on liver biopsy.
- Advent of directly acting antiviral agents (DAAs) has transformed therapeutic landscape. All oral, interferon-free regimens now available. DAAs have different mechanistic actions (see Table 4.20).
- Endpoint of therapy is undetectable HCV RNA at 12wk (SVR12) and/or 24wk (SVR24), after the end of treatment.
- Access to new DAAs currently limited to patients with advanced fibrosis/decompensated disease. Cost is an important consideration.
- SVR rates with DAAs >95%.

Acute hepatitis C.

Rare clinical diagnosis, but >95% SVR with antiviral therapy. Check HCV RNA every 4wk. Patients who remain viraemic should be treated within 3mo with sofosbuvir + ledipasvir (genotypes 1, 4, 5, and 6), or sofosbuvir + velpatasvir (all genotypes) for 8wk. Assess SVR at 12wk and 24wk post-treatment.

Chronic hepatitis C

- Treatment regimens constantly changing. For up-to-date recommendations visit the 🖱 EASL website.
- Special clinical scenarios in which treatment may be effective, but which require expert involvement are:
  - Patients with HIV/HCV co-infection.
  - Adults who have relapsed following previous treatment response.
  - Children with chronic hepatitis C.
  - HBsAg^{+} patients undergoing DAA therapy at risk of reactivation of HBV, and should be considered for nucleoside/nucleotide analogue prophylaxis until 12wk post-DAA. HBcAb positive patients should be monitored for reactivation.
- End-stage liver disease due to chronic hepatitis C remains an indication for orthotopic ➲ liver transplantation. Recurrence of HCV in grafted liver almost universal, with cirrhosis sometimes occurring at accelerated rate in these immunocompromised patients (up to 10% of patients within 5y of transplantation).
- Eradication of HCV in patients with advanced fibrosis and cirrhosis ↓ risk of ➲ hepatocellular carcinoma (although risk not abolished hence ongoing surveillance should continue).

Guidelines

🖱 EASL clinical practice guidelines for treatment of hepatitis C (2016).

🖱 AASLD recommendations for testing, managing, and treating hepatitis C (2016).

Table 4.20 Mode of action of antiviral agents for HCV

Class	Drug name	Activity	Mode of action
Interferons	Pegylated interferon alfa	All HCV genotypes	Induces immune response against HCV resulting in inhibition of viral replication
Ribavirin	Ribavirin	All HCV genotypes	Unclear but has direct and indirect effects on HCV virus replication
Directly acting antivirals (DAA)			
NS3/NS4A serine protease inhibitors	Boceprevir Simeprevir Telaprevir ABT-450	Genotype 1a and 1b	Prevent proteolytic processing of HCV polyprotein
NS5A inhibitors	Daclatasvir Ledipasvir Ombitasvir	All HCV genotypes	Prevent formation of replication complex
NS5B polymerase inhibitors (nucleot(s)ide analogues)	Sofosbuvir	All HCV genotypes	Inhibit RNA-dependent RNA polymerase competitively by binding to the catalytic site of HCV polymerase
NS5B polymerase inhibitors (non-nucleot(s)ide analogues)	Dasabuvir	Genotypes 1a and 1b	Inhibit RNA-dependent RNA polymerase by inhibition of the binding site of HCV polymerase

Hepatitis D virus (HDV)

- HDV, or delta virus, is a RNA virus that requires ➔ hepatitis B virus for complete virion assembly (5% HBV carriers co-infected with HDV).
- As with HBV infection, HDV may cause acute hepatitis (even ▲ **acute liver failure** ▲), asymptomatic viral carriage, or progressive chronic liver disease with cirrhosis and ➔ portal hypertension (more aggressive course of HDV/HBV co-infection than HBV alone). For uncertain reasons, HDV infection associated with lower risk of ➔ hepatocellular carcinoma than HBV infection alone.
- Presence of HBsAg necessary for diagnosis of hepatitis D. Anti-HDV IgM present in acute infection, and IgG antibodies appear in resolved or chronic infection. In contrast with HBV, IgM antibodies persist at high titre in chronic infection. Serum HDV RNA detectable by PCR in acute infection and chronic disease, but test not widely available.
- Vaccination against ➔ hepatitis B protects against HDV.
- Treatment options limited. Currently only pegylated interferon for 48wk has demonstrated on-treatment response rates of 17–47%. However, relapse after 24wk of treatment in 50%. Nucleoside/nucleotide analogue therapy should be considered in patients with ongoing HBV DNA replication.
- ➔ Liver transplantation may be required in decompensated HDV/HBV cirrhosis (again, post-transplant survival better for HDV/HBV co-infection than for HBV alone, possibly related to inhibitory effects of HDV on HBV).

Hepatitis E virus (HEV)

RNA virus endemic in India, Pakistan, Middle East, and SE Asia (accounts for >90% of major hepatitis outbreaks in India). Outbreaks increasingly recognized in Europe and UK. Four genotypes (1–4) identified. Virus spread by faecal–oral route in association with poor sanitation; genotype 3 zoonotic (porcine reservoir frequently identified). Transmission also possible from contaminated blood products.

Clinical features

- Incubation 15–65d.
- Most patients asymptomatic, but frequent manifestations include jaundice, fever, malaise, and myalgia.
- Extrahepatic manifestations include Guillain–Barré syndrome, encephalitis, myopathy, polyradiculopathy, and glomerulonephritis.
- Increased risk in pregnant ♀. Commonest cause of acute liver failure in pregnancy, especially 2nd and 3rd trimester.
- Now recognized as a cause of chronic hepatitis. ‘Super-infection’ can occur in patients with chronic liver disease, and ↑ risk of chronic infection in solid organ transplant recipients..

Diagnosis

- Detection of anti-HEV IgM.
- HEV RNA detectable in blood and stool (up to 2wk).

Treatment

- Acute HEV usually self-limiting in immunocompetent.
- Immunosuppression should be ↓ if possible in immunocompromised. → RIBAVIRIN 600mg od can be considered.
- ➲ Liver transplantation considered for ▲ **acute liver failure** ▲.

Hepatocellular carcinoma (HCC)

Epidemiology and pathogenesis

- 6th most common cancer globally, and >90% of primary liver cancers. Highest prevalence in China, SE Asia, and sub-Saharan Africa.
- 75–90% of patients with HCC have cirrhosis, and HCC develops in 1–8% of cirrhotics/y.
  - Chronic ➲ hepatitis B ↑ risk of HCC 100-fold.
  - Rare in ➲ hepatitis C in absence of cirrhosis.
  - HIV potentiates risk in patients with chronic viral hepatitis.
  - Less common if cirrhosis due to ➲ autoimmune hepatitis or ➲ primary biliary cholangitis.
  - Other risks include aflatoxins produced by fungi on nuts stored in damp conditions (e.g. common aetiology of HCC in N Africa and China), and potentially diabetes mellitus (likely through predisposition to ➲ non-alcoholic fatty liver disease).

Clinical features

- Pain, weight loss, anorexia, and malaise common. Some patients may be asymptomatic.
- Hepatomegaly common; hepatic bruit sometimes found.
- HCC may be precipitating cause of hepatic decompensation and ▲ **hepatic encephalopathy** ▲.
- 10% of patients present with variceal bleeding, which may be linked to ➲ portal vein thrombosis.

Investigations

- ➢ α-fetoprotein (αFP) ↑ in 70%, with levels >400ng/ml >95% specific for HCC (normal range <20ng/ml). However, high levels also seen during hepatitis flares (i.e. in association with ↑↑ ALT). >60% HCCs <4cm have αFP <200ng/ml (Box 4.32).
- US widely used in screening/surveillance, and first modality if ↑αFP (sensitivity 95% for 1.5–3cm HCCs). See Box 4.33 for differential diagnosis of mass lesions in liver.
- CT or MRI required. Typical features of HCC include hypervascular lesion in arterial phase with washout in portal venous or delayed phases. Only 1 imaging modality required for nodules >1cm.
- Liver biopsy confirms histological diagnosis, but avoided if resection an option because risk (albeit <2%) of needle-track seeding.

Box 4.32 Causes of ↑ αFP

- Hepatocellular carcinoma.
- Active hepatitis or cirrhosis.
- Non-seminomatous germ cell tumours of testis/ovary.
- Gastric or pancreatobiliary cancer (usually with liver metastases).
- Pregnancy.

Management

- Untreated, 3y survival for small HCC in non-cirrhotic liver is 45%.
- Barcelona Clinic Liver Cancer (BCLC) staging system recommended for prognostication and treatment allocation (see Fig. 4.12).
- Options include hepatic resection, liver transplantation, localized tumour ablation, or systemic chemotherapy.
  - Hepatic resection should be considered for solitary tumours with well-preserved liver function (normal Bn) and either hepatic venous pressure gradient ≤10mmHg or platelets ≥100 × 10^9/L.
  - ➔ Liver transplantation considered for cirrhotic patients with solitary HCC <5cm, or ≤3 lesions all <3cm ('Milan criteria'). These criteria result in 75% post-transplant 4y survival. Expansion of these criteria to single lesion of 6.5cm, or 2–3 nodules with largest 4.5cm and total tumour diameter 8cm (University of California at San Francisco (UCSF) criteria) result in 50% 1y survival.
  - In non-surgical candidates with localized HCCs, local ablation (e.g. percutaneous alcohol injection or radiofrequency ablation) may provide good palliation for lesions <5cm, and survival comparable with hepatic resection, with mortality largely correlated with underlying liver function.
  - Transcatheter chemoembolization (TACE) relies on inducing ischaemia in HCC and targeting chemotherapy, but contraindicated in decompensated cirrhosis and multifocal HCC.
  - Systemic chemotherapy regimens remain disappointing.
  - Sorafenib, an oral multityrosine kinase inhibitor, is the only drug that has demonstrated survival benefit in advanced HCC.
- Complications such as spontaneous rupture, capsular pain, obstructive jaundice, or malignant ascites should be managed with conventional measures. In addition:
  - Haemostasis following spontaneous rupture may be achieved by transarterial embolization (approach of choice in patients with preserved liver function without complete portal vein thrombosis); surgically; or by liver resection (reserved for small, easily accessible tumours in non-cirrhotic livers).
  - NSAIDs can be particularly effective for capsular pain, and dexamethasone 4–8mg PO/IV bd useful adjunct.
  - Paravertebral nerve blocks occasionally required for intractable pain.

Surveillance

HCC surveillance (6-monthly US and αFP) recommended in:

- Cirrhotic patients (including those awaiting liver transplantation).
- Non-cirrhotic HBV carriers with active hepatitis or family history of HCC.
- Non-cirrhotic patients with chronic HCV and advanced fibrosis.

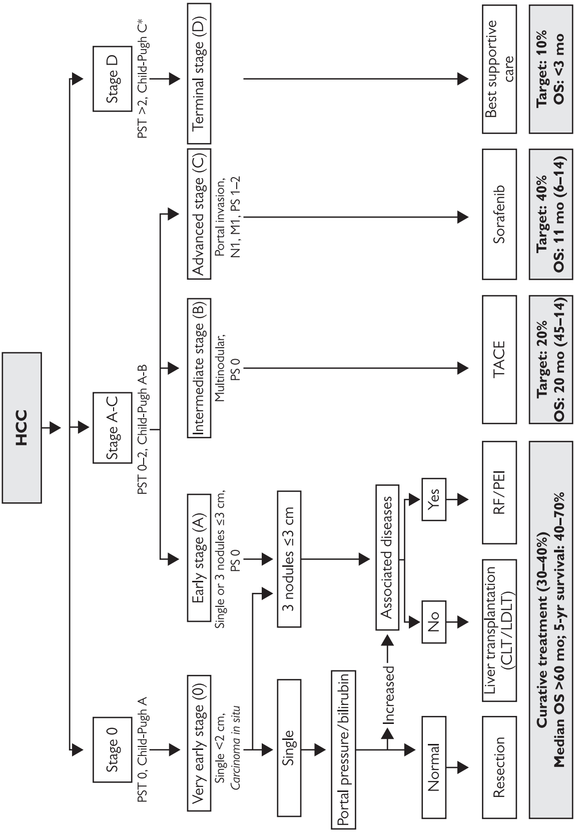
HCC
Stage 0
PST 0, Child-Pugh A
Stage A-C
PST 0–2, Child-Pugh A-B
Stage D
PST >2, Child-Pugh C*
Very early stage (0)
Single <2 cm,
Carcinoma in situ
Early stage (A)
Single or 3 nodules ≤3 cm,
PS 0
Intermediate stage (B)
Multinodular,
PS 0
Advanced stage (C)
Portal invasion,
N1, M1, PS 1–2
Terminal stage (D)
Single
3 nodules ≤3 cm
Portal pressure/bilirubin
Increased
Associated diseases
Normal
No
Yes
Resection
Liver transplantation
(CLT/LDLT)
RF/PEI
TACE
Sorafenib
Best supportive
care
Curative treatment (30–40%)
Median OS >60 mo; 5-yr survival: 40–70%
Target: 20%
OS: 20 mo (45–14)
Target: 40%
OS: 11 mo (6–14)
Target: 10%
OS: <3 mo

Fig. 4.12 Barcelona Clinic Liver Cancer staging system. Reproduced with permission from EASL clinical practice guidelines for management of chronic hepatitis B (2012).

Box 4.33 Causes of mass lesions in liver

- ➲ Hepatocellular carcinoma.
- Fibrolamellar carcinoma.
- Metastases (most common cause, due to e.g. ➲ colon, ➲ pancreas, ➲ gastric cancer, ➲ neuroendocrine tumour).
- Intrahepatic ➲ cholangiocarcinoma.
- ➲ Gallbladder carcinoma.
- ➲ Focal nodular hyperplasia.
- ➲ Nodular regenerative hyperplasia.
- Hepatic adenoma.
- ➲ Haemangioma.
- ➲ Liver abscess*.
- ➲ Hydatid disease*.
- ➲ Lymphoma.
- Angiosarcoma.
- Benign regenerative nodule.
- Simple cyst*.

* Cystic lesions.

Guidelines

✍ EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma (2012).

Hepatopulmonary syndrome (HPS)

Triad of hepatic dysfunction, arterial oxygenation defect (with or without hypoxaemia) and intrapulmonary vascular dilatation (IPVD). Can occur in cirrhotic and non-cirrhotic patients.

Clinical features

- Dyspnoea, platypnoea (dyspnoea made worse by standing) and orthodeoxia (hypoxaemia worsened by standing).
- Digital clubbing, cyanosis, spider naevi, and telangiectasia.

Diagnosis

- Demonstrate hypoxaemia (mild: PaO_2 ≥80mmHg; moderate: PaO_2 60–79mmHg; severe: PaO_2 50–59mmHg) and IPVD without evidence of intrinsic pulmonary disease.
- IPVD diagnosed using contrast-enhanced transthoracic echocardiography. Microbubbles appear in left heart 3–6 cycles after injection of contrast entering the right heart. ^{99}Tc-labelled macroaggregated albumin can also be used.

Management

- Limited treatment options. Long-term oxygen usually required.
- ➲ Liver transplant can result in improved oxygenation in selected patients.

Hepatorenal syndrome (HRS)

HRS should be considered as a possible cause of acute kidney injury (AKI) in patients with acute or chronic liver disease with portal hypertension. All patients presenting with renal dysfunction should have a renal screen performed. HRS is diagnosis of exclusion. ❗ A common clinical mistake is to assume that any 'liver' patient with renal impairment has hepatorenal syndrome, whereas the range of causes of renal dysfunction in cirrhotic patients is shown in Box 4.34. Overall, serum creatinine is poor marker of glomerular filtration due to ↓ hepatic creatinine production.

The pathological process in HRS is of splanchnic arterial vasodilatation followed by profound renal arteriolar vasoconstriction, leading to renal hypoperfusion in the setting of haemodynamic changes of decompensated liver disease (↑ heart rate, ↑ cardiac output, ↓ systemic vascular resistance, ↓ mean arterial pressure). Vasodilatation is thought to be mediated by increased nitric oxide production.

- **Type 1 HRS** occurs acutely, often in conjunction with acute liver disease or decompensation of cirrhosis. Often associated with marked jaundice and coagulopathy. Defined as twofold ↑ in serum creatinine in <2wk.
- **Type 2 HRS** is more chronic and insidious. Usually occurs in patients with refractory ascites and relatively mild jaundice.

Diagnosis

- Clinical diagnosis based around major diagnostic criteria:
  - Serum creatinine > 133μmol/L (1.5mg/dL).
  - No improvement in creatinine after at least 2d of diuretic withdrawal and volume expansion with albumin.
  - Absence of shock.
  - Other causes of renal impairment excluded (hypovolaemia, bacterial sepsis, nephrotoxic drugs).
  - Proteinuria <0.5 g/d.
  - Normal renal tract US.
- Note that low urinary Na^+ is no longer required for diagnosis.
- Precipitants of HRS include sepsis (in particular SBP) and GI bleed.

Management

- Stop all potentially nephrotoxic drugs (e.g. diuretics).
- Correct hypovolaemia. 💣Debate continues as to relative merit of albumin over other volume expanders, but may have specific immunomodulatory effects.
- Search for and treat sepsis (common precipitant of liver decompensation). Send blood, urine, and ascitic fluid for culture.
- Drain ascites if tense (see ⊳ paracentesis).
- Consider terlipressin 1mg IV qds.
- Consider renal support (usually haemofiltration) if likely improvement in liver function/liver transplantation. Note that HRS rarely resolves unless liver function improves, and has 50–95% mortality dependent on aetiology.
- ➲ Liver support devices may improve biochemistry in this setting, but definite benefit on clinical outcome not confirmed.
- Definitive treatment, where indicated, is ➲ liver transplantation.

Box 4.34 Causes of renal dysfunction in patient with liver disease

- Acute kidney injury secondary to volume depletion or sepsis.
- Hepatorenal syndrome.
- Nephrotoxic drugs (e.g. NSAIDs, aminoglycosides).
- Glomerulonephritis complicating liver disease (IgA nephropathy).
- Renal dysfunction and liver disease occurring together as part of systemic illness (e.g. polycystic liver and kidney disease, membranous glomerulonephropathy due to ➔ hepatitis B).
- Chronic kidney disease coexisting in patient with cirrhosis.

Hepcidin

Peptide hormone that regulates plasma iron concentrations.[4] Primarily produced by hepatocytes, and acts on ferroportin, a cellular iron exporter. Ferroportin mediates transfer of iron into blood from duodenal enterocytes (hence regulating dietary absorption), as well as hepatocytes and macrophages. Chronically ↑ hepcidin leads to development of anaemia. Conversely, chronic deficiency results in iron overload, and hepcidin deficiency is the pathogenic cause of most cases of hereditary ➔ haemochromatosis (through deleterious mutations in its regulators *HFE*, *TFR2* or *HJV*, or hepcidin itself). The major stimulus for hepcidin production is iron itself (as part of negative regulatory mechanism), but also an acute phase reactant, and ↑ in inflammatory states via IL-6. Several hepcidin agonists/mimics and antagonists currently under investigation as potential therapeutics for iron deficiency, anaemia of chronic disease, and iron overload disorders.

Hereditary angio-oedema

Aetiology and pathogenesis

Autosomal dominant, affecting 1/50,000 people. Caused by deficiency (type 1) or functional impairment (type 2) in C1 esterase inhibitor, a regulator of factors XIIa, XIIf, and kallikrein. Results in overproduction of bradykinin, leading to ↑ vascular permeability and angio-oedema. First recognized as syndrome by Osler in 1888.

Clinical features

- Recurrent oedema of skin and mucous membranes, without urticaria. Persists for days. Although can be tingling or burning at onset, lesions are painless and, unlike urticaria, pruritus is absent.
- Onset usually in childhood and family history usually present.
- Attacks may be precipitated by local trauma, dental extractions, surgery, menstruation, use of OCP or ACE inhibitors, or psychological stress. However, often no trigger can be identified.

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[4] Ruchala P & Nemeth E (2014). *Trends Pharmacol Sci* **35**: 155–61.

- GI involvement includes colicky pain, watery diarrhoea, and vomiting. Can cause ▲ **intestinal obstruction** ▲. Fluid loss can lead to hypotension and shock. Fever and leucocytosis absent, bowel sounds may be ↑, and there is no peritonism.
- Laryngeal attacks infrequent but oedema can obstruct airway.

Diagnosis

- Often missed at first by clinicians. Risk of labelling patients as 'functional' or 'drug-seeking', or performing unnecessary investigations.
- Blood tests:
  - ↓C4 (low in 95% of asymptomatic patients, and almost invariably during attack).[5]
  - ↓C1q (low in acquired deficiency).
  - ↓C1 esterase inhibitor levels or activity.
- AXR/CT/US during abdominal attack will show intestinal wall thickening due to oedema ± dilated loops of bowel.
- Avoid endoscopy if possible as risk of inducing laryngeal oedema.

Treatment

- Antihistamines, corticosteroids, and adrenaline are not effective.
- Plasma-derived C1 esterase inhibitor concentrate can abort attack.[6] Dose depends on preparation.
- Data also support efficacy of icatibant (bradykinin receptor antagonist) 30mg SC single dose.
- Promising trial data available for kallikrein inhibitors (ecallantide) and recombinant C1 esterase inhibitor (conestat alfa).
- Prophylaxis:
  - Pre-medication with C1 esterase inhibitor concentrate ↓ risk of provoking attack during interventional procedures such as upper GI endoscopy. Provide dose within 24h prior to procedure. Use for any major intervention. If not used for minor procedure, ensure availability in case of attack.
  - Anabolic steroids (danazol, stanozolol) can prevent attacks. May have actions other than ↑ levels of C1 esterase inhibitor as patients often respond to low doses (insufficient to ↑ complement levels). Doses tailored to clinical rather than biological response.

Hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu syndrome)

Aetiology and pathogenesis

Rendu was first to describe condition in 1896 ∴ should really be Rendu–Osler–Weber syndrome. Autosomal dominant. Disease affects capillaries, venules, and less commonly arterioles. Pulmonary AV malformations occur in 20%, especially in families with HHT1, caused by mutation in endoglin gene on chromosome 9; this can lead to high-output cardiac failure. AV malformations occur less commonly in cerebral and hepatic circulations. HHT2 maps to chromosome 12, where mutations have been identified in *ALK1* gene.

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[5] Longhurst HJ & Nzeako UC (2012). *Br J Hosp Med* **73**: 148–54.

[6] Bork K (2016). *Clin Rev Allergy Immunol* **51**: 183–92.

Clinical features

- Characterized by telangiectasia of skin and mucous membranes (Plate 3).
- Most common presentation is with epistaxis at puberty.
- Cutaneous telangiectasia can appear later, usually before age 20.
- Severe GI bleeds occur, usually after age 40. Melaena most common manifestation. Telangiectasia easily seen at endoscopy. Angiography may show arteriovenous (AV) malformations.

Diagnosis

- Clinical, based on 4 cardinal features (2 present = possible; 3–4 = definite).
  - Spontaneous recurrent epistaxis.
  - Multiple telangiectasias.
  - Proven visceral AVM.
  - 1st degree affected relative.
- Genetic diagnosis not required, but may be helpful to confirm diagnosis in "possible" cases, or avoid screening children of affected parent if causal mutation in that family known.

Management

Treatment difficult. Options include oestrogens, aminocaproic acid, endoscopic ablation, and bowel resection. Endoscopic ablation, including use of ➢ argon plasma coagulation and thermal contact devices, probably most effective.

Hereditary non-polyposis colon cancer (HNPCC)

Aetiology and pathogenesis

Also known as Lynch syndrome. Autosomal dominant, causing ≈5% of ➲ colon cancers. Cancer arises in discrete adenomas but polyposis does not occur. About 80% caused by germline mutations in DNA mismatch repair genes and include *hMSH2* on chromosome 2 (40–50%) and *hMLH1* on chromosome 3 (20–30%).

Clinical features

Comparison of HNPCC with sporadic cancers shown in Table 4.21. Can be divided into Lynch syndrome I (familial colon cancer) and Lynch syndrome II (HNPCC associated with other cancers of GI or reproductive systems).

Diagnosis

Still made on clinical grounds, but likely genetic testing will become increasingly available. Best known are 'Amsterdam criteria' (Box 4.35), although these do not account for frequent occurrence of non-colonic cancers in these families. May be early onset endometrial, ovarian, upper urinary tract, small intestinal, and stomach cancer.

Management

- Treatment broadly similar to sporadic cancer, although approach adapted to account for high rate of synchronous and metachronous cancers (3%/y).
- Lifetime risk of colorectal cancer 50%: start colonoscopic screening at 25y, or 5y before earliest colon cancer in family. Repeat every 2y. Upper GI screening also required.

Box 4.35 Amsterdam II criteria for hereditary non-polyposis colorectal cancer

At least 3 relatives with HNPCC-associated cancer (colorectal cancer, cancer of endometrium, small bowel, ureter, or renal pelvis), plus all of the following:

- One affected patient is 1st-degree relative of the other two.
- Two or more successive generations affected.
- One or more cases of colon cancer diagnosed before age 50.
- Familial adenomatous polyposis (FAP) excluded.
- Tumours verified by pathological examination.

Hereditary pancreatitis

- Autosomal dominant, associated with specific genetic defects. Rare: prevalence 0.3/100,000. Familial pancreatitis is a more generic term, used when more members in family are affected with pancreatitis than expected, but without an obvious cause.

Table 4.21 Clinical features of HNPCC compared with sporadic colon cancer

	HNPCC	Sporadic cancer
Mean age at diagnosis (y)	45	65
Multiple cancers	35%	4–11%
Proximal location	72%	35%
Excess malignancy at other sites	Yes	No
Mucinous tumours	Common	Rare
Prognosis	Favourable	Variable

Reproduced with permission from Feldman M *et al*. (1998). *Sleisenger and Fordtran's Gastro-intestinal and Liver Disease* (7th edn). W.B. Saunders.

- Range of mutations identified (e.g. serine protease 1 gene *PRSS1*, serine protease inhibitor Kazal type 1 gene *SPINK1*, and cystic fibrosis transmembrane conductance regulator *CFTR*). R122H mutation of *PRSS1* are most common.
- Pathogenesis involves trypsinogen conversion to trypsin, which then activates pancreatic proenzymes (except amylase and lipase). Trypsinogen conversion is tightly controlled, hence gene mutations associated with are excess production, autodigestion, and pancreatitis.
- Genetic testing available, and 80% with *PRSS1* R122H or N29I mutations will develop pancreatitis (i.e. 80% penetrance). Negative test in family with known mutation eliminates risk.
- Recurrent episodes of pancreatitis begin at age <40y (mean 10y), with chronic pancreatitis developing in 50%. Standard management for ➲ acute and ➲ chronic pancreatitis applies.
- Cumulative risk of ➲ pancreatic cancer may be >40% by 70y. Smoking further ↑ risk.
- Screening for cancer usually begins at 40y, and includes initial CT, EUS, CA19-9, and glucose.
    - If no evidence of malignancy, then ERCP and pancreatic juice analysis (p53, Kras, p16 methylation). If negative, 3-yearly CT.
    - If positive molecular analysis (or not done), close monitoring with annual imaging.

Hereditary polyposis

Inherited polyposis can be broadly considered in terms of adenomatous and hamartomatous syndromes.

Adenomatous polyposis syndromes

Range of inherited adenomatous polyposis syndromes characterized by development of large numbers of adenomatous polyps in colon, and high risk of ➲ colon cancer:

- ➲ Familial adenomatous polyposis (FAP).
- ➲ Gardner's syndrome. Similar intestinal polyp pattern to FAP, with additional thyroid/adrenal tumours, fibromas, desmoid tumours, and bone tumours. Associated with *APC* gene.
- ➲ Turcot's syndrome. Colonic adenomas (usually fewer than in FAP), with medulloblastoma.

Hamartomatous polyposis syndromes

Hamartomas are of mesenchymal origin, and carry lower risk of malignant change than adenomas. However, ↑ cancer risk (GI and non-GI) seen in these conditions:

- ➲ Peutz–Jeghers syndrome.
- ➲ Juvenile polyposis syndrome.

- ➔ Cowden's disease.

See also ➔ hereditary non-polyposis colon cancer (HNPCC) and ➔ Cronkite–Canada syndrome (rare non-inherited cause of polyposis).

Herpes simplex virus (HSV)

DNA virus, causing painful vesicles with erythematous bases in skin, mouth, oesophagus, colon, and rectum. Resolution followed by latency in nerve roots and ganglia supplying affected regions. Transmission oral-to-oral, or during sexual intercourse.

Clinical features

HSV-1 generally associated with orolabial and ocular lesions. HSV-2 accounts for most anogenital lesions.

- **Orolabial infection** 90% of cases of primary herpetic gingivostomatitis occur before puberty. Recurrent cold sores common and precipitated by illness, sunlight, or stress.
- **Oesophagitis** Presents with odynophagia or ▲ **upper GI bleeding** ▲ from ulceration. Mid-distal oesophagus most commonly affected. Immunosuppression predisposes to infection, particularly HIV with CD4 count <200/mm^3 (see ➔ HIV and the gut) and allogeneic stem cell transplant (usually during pre-engraftment). Complications of untreated disease include mucosal necrosis, oesophageal perforation, haemorrhage, strictures, and ➔ tracheo-oesophageal fistula.
- **Colitis** Causes bloody diarrhoea in immunocompromised patients.
- **Proctitis** Usually a primary infection, with symptoms 1–3wk after exposure. Presents with severe anorectal pain, tenesmus, constipation, and ulceration. May be associated fever, dysuria, and inguinal lymphadenopathy. Can reactivate, although subsequent episodes tend to be less severe.
- **Perianal disease** Painful vesicles. When resolving, lesions crust, then tend to heal within 2wk.
- **Hepatitis** Most commonly arises in context of immunocompromise, but can affect immune competent. Pregnant ♀ appear at particular risk. Presentation non-specific and can cause ▲ **acute liver failure** ▲. High index of suspicion required. Consider if oromucosal lesions or risk factors for HSV present.
- **Pancreatitis** Rare but recognized viral cause of pancreatitis.

Diagnosis

- Characteristic appearance of orolabial and genital vesicles.
- Luminal disease usually diagnosed endoscopically (see Plate 13).
  - May find vesicles, whose centres slough to form 'volcano' lesions. Often see mucopurulent exudate. Ulcers can develop.
  - Biopsies should include epithelium, and can show multinucleated giant cells ± intranuclear inclusions.
  - Virus can be detected by culture or immunostaining within 24h. PCR has highest sensitivity.

- Serology may give clues to diagnosis but can be negative during early infection. Consider screening for HIV co-infection.
- Diagnosis of hepatic or pancreatic disease usually made on serology or viral PCR on blood. ➲ Liver biopsy indicated if clinical uncertainty; may show intranuclear viral inclusions, and positive HSV immunohistochemistry.

Treatment

- Mainly symptomatic, with oral analgesia or topical local anaesthetics for pain relief. Avoid steroid ointments.
- Episodic antiviral therapy can be considered in immune competent, but does not eradicate HSV or ↓ risk of recurrence. Does provide benefit in immunocompromised, as shortens duration of symptoms as well as period of viral shedding.[7] Treatment generally with → ACICLOVIR, although resistant strains beginning to emerge.
  - **Orolabial disease** Topical → ACICLOVIR 5% cream applied to lesions every 4h for 5–10d speeds healing and ↓ severity.
  - **Oesophagitis** → ACICLOVIR 5–10mg/kg IV tds (while unable to take oral medication), followed by 400mg PO 5/d, for 14d.
  - **Proctocolitis** → ACICLOVIR 400mg PO 5/d, or 5–10mg/kg IV if severe, for 7–14d.
- Reduce frequency of aciclovir administration in renal impairment.
- Alternative to aciclovir is valaciclovir 1g PO bd.
- Resistant viruses may respond to foscarnet 90mg/kg IV bd.
- Counsel regarding safe sex practices if risk of transmission.

Herpes zoster

Neurotropic herpesvirus, causing chickenpox and shingles. Highly infectious. Predominantly acquired in childhood but lifelong latency and can reactivate in local nerve distributions (including enteric and autonomic nerves), causing pain and hyperalgesia.

GI manifestations

- Severe ➲ oesophagitis or ➲ gastric ulcer in immunocompromised.
- Hepatitis.
- T7–L1 nerve involvement can cause abdominal pain (may commence 2–3/7 before skin lesions appear).
- Sacral nerve root involvement can cause constipation and pain on defaecation.
- Suggested to underlie some cases of pseudo-obstruction and unexplained abdominal pain, due to enteric nerve involvement.
- Risk of reactivation in patients on biologic therapy or profound immunosuppression.

Diagnosis

- Viral culture, immunostaining, or PCR.
- Presence of characteristic skin lesions can be sufficient for clinical diagnosis (rare with HSV).

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[7] Hoentjen F & Rubin DT (2012). *Dig Dis Sci* **57**: 269–73.

Treatment

- → ACICLOVIR 800mg PO 5/d for mild-moderate disease, or 5mg/kg IV tds severe disease (or unable to swallow tablets), for 5d. Increase to 10mg/kg in immunocompromised; may require for up to 14d.

Hiatus hernia

Two types: **sliding hernia**, when gastro-oesophageal junction and some part of stomach displaced above diaphragm (most common type, accounting for ≈95%; usually small and of no clinical significance); and **para-oesophageal (rolling) hernia**, when stomach protrudes through oesophageal hiatus alongside oesophagus.

Clinical features

Most sliding hernias small but can predispose to gastro-oesophageal reflux (see also ► Approach to dyspepsia and gastro-oesophageal reflux). Large hernias may develop Cameron ulcers, usually on lesser curve at level of hiatus: they can cause upper GI bleeding or iron deficiency anaemia.

Treatment

Simple sliding hiatus hernias do not need treatment. Giant or para-oesophageal hernias may require surgery (see ➢ antireflux procedures).

Hirschsprung's disease

Named after Harald Hirschsprung (1830–1916), the first paediatrician to be appointed in Denmark. Important cause of congenital ➲ megacolon. Occurs in 1/ 5,000 live births. Autosomal dominant or recessive, with 30% penetration. Absence of ganglion cells from myenteric and submucosal plexuses characteristic, extending proximally from internal anal sphincter. Divided into short segment disease (≈80% of cases) confined to rectosigmoid, or long segment extending more proximally and occasionally including entire colon.

Clinical features

Usually presents after birth with failure to pass meconium, and later in childhood with recurrent faecal impaction, constipation, and malnutrition. May be complicated by enterocolitis in infancy. Overflow rarely occurs. Associated with ➲ multiple endocrine neoplasia (MEN)-2 and ➲ Down syndrome. Occurs more often in ♂ than ♀ (4:1); however, ratio in long-segment disease ↓ to 2:1.

Investigation

- Barium enema may show narrowed distal rectum free from faeces, with proximal colonic dilatation.
- Proctosigmoidoscopy normal, with deep rectal biopsy showing absence of ganglion cells in submucosa. Note, biopsy should be taken at least 1.5cm above dentate line as normal for most distal portion of rectum to be aganglionic.
- Anorectal manometry may show resting internal anal sphincter pressure normal or increased, and internal anal sphincter contracts in response to rectal distension (rather than relaxes, with compensatory external sphincter contraction, as per normal 'rectal inhibitory reflex').

Management

Primary treatment surgical, aimed at excising aganglionic segment. Colostomy prior to definitive operation may be required. Persistent problems with soiling may occur in ~10%.

HIV and the gut

Background and aetiology

- All areas of GI tract may be affected (see also ➲ HIV and the liver).
- Before development of HAART, opportunistic infections associated with immunocompromise were major cause of GI problems. Now, drug-induced side effects and non-opportunistic diseases more common (Table 4.22).
- Complications vary according to mode of HIV acquisition, with differences between heterosexual and vertical infection, IV drug misuse, and MSM.
- Co-infection with HIV and ➲ hepatitis B and ➲ hepatitis C common, as is non-pathogenic colonization of GI tract (so direct demonstration of microbial tissue invasion remains gold standard).
- Involve HIV term early. Successful HAART often sufficient to induce remission and prevent relapse of most presentations, or change in drug regimen may be required if symptoms are related to therapeutics. Around 15% of patients with AIDS started on HAART develop immune reconstitution inflammatory syndrome (IRIS), which can have up to 4% mortality. Risk highest in patients with CD4 counts $<50/mm^3$ and underlying ➲ cytomegalovirus (CMV), ➲ tuberculosis, or ➲ Kaposi's sarcoma.

Clinical features

Broad categories of presentation include:

- **Oesophageal disease**
  - ➲ Oesophagitis develops in ≈10% of HIV-infected patients (similar to background population levels), most commonly due to ➲ gastro-oesophageal reflux disease.
  - Dysphagia or odynophagia suggest oesophageal ➲ candidiasis or ulceration (e.g. ➲ cytomegalovirus, ➲ herpes simplex virus).

  - Drug causes include zidovudine and doxycycline.
  - Ulceration can occur during initial HIV seroconversion.
- **Abdominal pain**
  - Any cause of this in non-HIV patient can, of course, be culprit.
  - Inflammation, ulceration, or perforation at any point in GI tract may be caused by range of pathogens, including CMV, ➲ tuberculosis, and *Mycobacterium avium* complex.
  - ➲ Acute pancreatitis may be due to HAART (particularly didanosine and stavudine; now rarely used in UK but often prescribed in Eastern Europe and sub-Saharan Africa, so need to consider in patients recently arriving from these locations), CMV, or infiltration by Kaposi's sarcoma.
- **Diarrhoea**
  - Occurred in 90% of patients in pre-HAART era. Still common, but now principally related to side effects of HAART (up to 70% of cases, particularly with protease inhibitors),[8] and causes not related to opportunistic infection/malignancy.
  - Profound immunocompromise (CD4 <200/mm^3) predisposes to ➲ coccidia, ➲ microsporidia, ➲ cytomegalovirus, ➲ tuberculosis, and *Mycobacterium avium* complex.
  - Oroanal intercourse is a risk factor for bacterial infections such as ➲ *Salmonella*, ➲ *Shigella*, and ➲ *Campylobacter*, as well as ➲ *Giardia*. Can develop cyclic reinfection if partner not treated.
  - Increasing numbers of patients have both ➲ Crohn's disease or ➲ ulcerative colitis and HIV. Long-term follow-up data suggest lower IBD relapses rates as CD4 counts fall. Classical immunosuppressants and biologics have been used in this population, mostly with successful outcomes and low burden of infectious complications, but close monitoring advised (particularly with newer agents).[9]
  - HIV enteropathy is a chronic inflammatory bowel disease not apparently attributable to other infections. Diagnosis of exclusion. Histology shows non-specific chronic inflammatory infiltrate in small and large bowel, with a preponderance of CD8 T cells, and villous flattening in duodenal biopsies.
- **Anorectal disease** Most common in MSM with HIV.
  - ↑ risk of viral warts (condylomata acuminata) and anal squamous cell carcinoma related to HPV.
  - *Chlamydia trachomatis*, *Neisseria gonorrhoea*, and *Treponema pallidum* can cause proctitis. Subtype of *Chlamydia* infection, lymphogranuloma venereum (LGV), caused by serovars L1-L3 now common; proctocolitis can take years to develop.
- **Neoplasia** Both ➲ Kaposi's sarcoma (due to HHV-8 infection) and non-Hodgkin's ➲ lymphoma can involve GI tract. May present with diarrhoea, bleeding, or obstruction. With Kaposi's sarcoma, oral violaceous lesions on palate predict visceral involvement.

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[8] Clay PG & Crutchley RD (2014). *Infect Dis Ther* **3**: 103–22.

[9] Ho TH *et al*. (2014). *Aliment Pharmacol Ther* **40**: 1171–86.

Investigation

- CD4 count guides investigation and differential diagnosis (opportunistic infection unlikely if >200/mm^3).
- Upper GI endoscopy required for oesophageal disease.
- In patients with diarrhoea, stepwise diagnostic work-up appropriate, as intensive screening does not detect significantly more treatable disorders, and non-specific treatment often effective:
  - Three stool samples for MC&S, and *C. difficile* toxin.
  - Peripheral blood cultures if febrile.
  - If CD4 <200/mm^3, blood cultures for mycobacteria, and stool samples for modified acid-fast stain or immunofluorescence, and modified trichrome stain for ➲ *Coccidia*.
  - If above negative, non-bloody diarrhoea, normal inflammatory markers, and CD4 >200/mm^3, can provide empiric antidiarrhoeal therapy (e.g. loperamide 2–4mg PO, up to qds). Empiric tinidazole 2g PO stat, often repeated after 1 wk, may be provided if ➲ *Giardia* suspected clinically, particularly in MSM.
  - Otherwise, perform flexible sigmoidoscopy to examine for CMV colitis (histology and immunostaining) and mycobacteria (histology and culture). Save additional sample in glutaraldehyde for electron microscopy if ➲ microsporidia suspected. Classic appearances may suggest diagnosis (e.g. large deep oesophageal ulcers due to CMV), but histology necessary. Vital that pathologists provided with details of HIV status, CD4 count, and suspected diagnosis. Check with referring clinicians regarding special requirements (e.g. biopsies into viral culture medium).
  - Rectal swabs for gonorrhoea and *Chlamydia* if history of receptive anal intercourse. PCR sensitive and specific.
  - If above non-diagnostic and CD4 <200/mm, request OGD and colonoscopy, with biopsies.

Management

- In patients presenting with opportunistic infection, commencement of HAART with immune reconstitution may negate necessity of antimicrobials for opportunistic infection (e.g. ➲ *Cryptosporidium*).
- Candidal oesophagitis treated with fluconazole 100mg PO OD for 7d. Maintenance/prophylaxis often required when CD4 <100/mm^3.
- Active CMV treated with 2–3wk course of → GANCICLOVIR IV.
- Idiopathic ulceration responds well to oral or intralesional steroids.
- Treatment of diarrhoea depends on isolating cause:
  - Enteric pathogens (e.g. ➲ *Salmonella*, ➲ *Shigella*, ➲ *Giardia*) treated with standard antibiotics.
  - Treatment for protozoal infections (e.g. ➲ *Cryptosporidium*) less effective, particularly if low CD4.
  - Treat lymphogranuloma venereum with doxycycline 100mg PO bd for 3wk.
  - Data limited for HIV enteropathy, but small case series suggest therapeutic responses to standard ➲ inflammatory bowel disease immunosuppressants and, possibly, institution of HAART.

Table 4.22 Common GI problems in HIV patients and their causes

Cause	Comment
Oesophageal disease (dysphagia/odynophagia)	
Candida albicans	➔ Oesophagitis usually linked with oral thrush. Suggests CD4 <200/mm^3
➔ Cytomegalovirus (CMV)	Large deep ulcers
Idiopathic ulcers	Small aphthous ulcers. Usually when CD4 <200/mm^3
➔ Herpes simplex virus (HSV)	Diffuse shallow ulcers
Kaposi's sarcoma, lymphoma	Often develop in oral cavity
Diarrhoea	
Bacterial: ➔ *Salmonella*, ➔ *Shigella*, ➔ *Campylobacter*, ➔ *Clostridioides difficile*, ➔ *Mycobacterium tuberculosis* (MTB)/*avium complex* (MAC), ➔ Bacterial overgrowth	*Salmonella* and *Shigella* more common in HIV patient, even on HAART. MAC most commonly identified GI opportunistic infection if low CD4 count. Acid-fast staining of biopsies
Protozoal: *Cryptosporidium, Microsporidium, Entamoeba,* ➔ hydatid	Oocytes of *Cryptosporidium* found on faecal smears. Treatment difficult, but may improve with HAART
Fungal: *Histoplasma, Cryptococcosis*	Diffuse colitis with histoplasmosis. Treatment with amphotericin B
Viral: ➔ Cytomegalovirus, ➔ Herpes simplex virus, ➔ adenovirus	CMV colitis in 5–10% with AIDS. Mucosal ulceration with inclusion bodies on histology.
'HIV enteropathy'	Chronic diarrhoea where no other cause found. Increasingly uncommon with more intensive investigation
Drugs: e.g. protease inhibitors	Diarrhoea mild/moderate, no weight loss
Kaposi's sarcoma (KS), lymphoma	KS may cause ulceration and chronic diarrhoea, but usually asymptomatic
➔ ***Pancreatic insufficiency***	
Anorectal disease	
Chlamydia trachomatis, lymphogranuloma venereum (LGV), *Neisseria gonorrhoeae*	Most common in MSM
➔ Herpes simplex virus	Perianal ulceration and proctitis
Human papilloma virus	Causes anal warts, linked to anal cancer
Idiopathic ulcers	Usually when CD4 <200/mm^3

  - If no treatable specific cause found, symptomatic treatment with → LOPERAMIDE 2–4mg PO qds appropriate.
- Treatment of neoplasia requires involvement of specialist oncology team. Potential options include surgical resection, immunomodulation (e.g. interferon), chemotherapy (will require prophylaxis for opportunistic infections; liaise closely with HIV team), and radiotherapy. Initiation of HAART improves prognosis. Full staging (imaging and bone marrow examination) mandatory.

HIV and the liver

Background and aetiology

Abnormal LFTs common (>80%) in HIV-infected patients. The following account for ≈80%:

- **Coexistent liver disease**. Viral hepatitis (➲ hepatitis B and ➲ hepatitis C) due to similar modes of acquisition, and have accelerated fibrosis rates compared to non-HIV-infected patients. Acute exacerbation of liver disease may occur following start of anti-HIV treatment as an IRIS against hepatitis B.
- **Alcohol**. Progressive ↑ in number of patients drinking excessively.
- ➲ **Drug-induced liver injury**. Common with HAART, as well as drugs to treat opportunistic infections. May be asymptomatic, and therefore under-reported. Due to combination therapies, determining culprit drug can be difficult. Patterns of injury include hypersensitivity (e.g. nevirapine, abacavir), idiosyncratic hepatotoxicity, mitochondrial toxicity (e.g. didanosine, stavudine), immune reconstitution syndrome, and hepatic steatosis. Non-cirrhotic ➲ portal hypertension has also been linked with HAART (e.g. didanosine).
- **Immunosuppression-related infection** (e.g. CD4 <100/mm^3), such as *M. avium intercellulare* (MAI), *M. tuberculosis* (MTB), or fungal infection (e.g. *Histoplasma capsulatum*).
- ➲ **Hepatocellular carcinoma**. Likely to ↑ due to co-infection with HBV and HCV.
- **Biliary disease**. HIV cholangiopathy (diffuse ➲ biliary strictures similar to ➲ primary sclerosing cholangitis, or distal biliary stricture/papillitis). Associated with low CD4 count, and with CMV and cryptosporidiosis. Rare with use of HAART
- **Tumours** (non-Hodgkin's ➲ lymphoma and ➲ Kaposi's sarcoma). Extremely rare.

Investigations

- In view of high frequency of LFT derangement, clinical balance needed between not missing important/reversible liver disease, and exposing

otherwise well patient to invasive tests. Baseline LFTs required in all patients.
- See ▶ Approaches to recent-onset jaundice and ▶ Approach to well patients with abnormal liver tests. Viral serology should be performed in all cases.
- US or CT may exclude biliary dilatation or liver masses.
- ERCP may be necessary to diagnose HIV cholangiopathy.
- Liver biopsy abnormalities in 90% (e.g. ➲ hepatic granulomas, steatosis), but 'new' diagnoses only made in 8% of biopsies (e.g. ➲ Kaposi's sarcoma, mycobacteria).

Management

- Depends on making specific diagnosis.
- ➲ Hepatitis B co-infection usually treated with combination treatment, including agents with dual action on HIV and HBV (e.g. lamivudine and tenofovir)
- LFTs should be regularly monitored during HAART (especially 1st 8wk, and with reverse transcriptase inhibitors), and stopped if signs of significant hepatotoxicity (e.g. serum ALT >5× ULN).
- ➲ Liver transplantation not contraindicated in HIV-infected patients. Poor outcomes described in HIV/HCV co-infection, although may improve with new directly acting antivirals for HCV.

Hookworms

See: ➲ Round worms.

Hydatid disease (see Plate 38)

Epidemiology and pathogenesis

Disease can be cystic (caused by *Echinococcus granulosus*) or alveolar (caused by *E. multilocularis*). Most commonly seen in farming or rural communities, where humans are accidental hosts for *E. granulosus*, whose life-cycle usually involves ingestion of eggs by definite host (carnivore, e.g. dog) from infected intermediate host (e.g. sheep).

Clinical features

Cystic echinococcosis affects liver (75% of cases), lungs (25%), and more rarely bones, kidneys, and brain. Many cysts asymptomatic, but may cause symptoms due to mass effect (obstructive jaundice, abdominal pain) or cyst complications (rupture with anaphylaxis, secondary infection).

Investigations

- Echinococcus ELISA 90% sensitive for hepatic echinococcosis.
- Eosinophilia in 25%.
- LFTs may be ↑ in hepatic disease.
- CT 98% accurate, and highly sensitive at demonstrating characteristic daughter cysts.

Management

- Suspected hydatid cysts should not be aspirated, as leakage of contents can cause anaphylaxis or dissemination of disease.
- Treatment is with high-dose albendazole for several weeks/months to sterilize cysts in cystic disease.
- Surgery is optimal approach, as only 30% cured with medical therapy alone. Options include cystectomy alone, or partial resection of affected organ. Pre-operatively, give albendazole 400mg PO bd for minimum of 14d (although if clinical condition allows, prolonged therapy for several months associated with lower complication rate), and add in praziquantel 20mg/kg PO bd 2 wk prior to intervention.
- If surgery not an option, the 'PAIR' technique (puncture-aspiration-injection-reaspiration) of aspiration of cyst contents and injection of scolicidal agent followed by isotonic saline, in conjunction with oral antimicrobial treatment (albendazole 400mg PO bd for at least 1mo over peri-procedural period, with 2-weekly monitoring of FBC and LFTs), may be effective.
- If cyst rupture suspected, give both praziquantel and albendazole.
- Prognosis generally good, although recurrence up to 30%.

Hydrogen breath test

See: ➔ 'Breath tests', p. 152.

Hypogammaglobulinaemia

See: ➔ Immunoglobulin deficiency.

Section 4

I

Ileal pouch–anal anastomosis (IPAA): see ▶ ‘Ileal pouch–anal anastomosis’ (p. 190) *416*

Ileostomy: see ▶ ‘Ileostomy’ (p. 188) *416*

Ileus *416*

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Ileal pouch–anal anastomosis (IPAA)

see: ▷ 'Ileal pouch–anal anastomosis' (p. 190).

Ileostomy

see: ▷ 'Ileostomy' (p. 188).

Ileus

This is the failure of forward passage of intestinal contents, in the absence of mechanical obstruction. There are several common causes in hospitalized patients (Box 4.36).

Intestinal motility may be impaired after abdominal surgery or injury. Small bowel motility usually returns in 24h, followed by gastric motility in 2d and colonic motility in 3–5d. Duration of operation and degree of manipulation do not appear to influence duration of ileus.

Clinical features

Poorly localized abdominal pain. Nausea, vomiting, and ↓/absent bowel sounds. Differentiation from obstruction usually possible based on gas in stomach, small intestine, and colon on plain AXR. Passage of contrast, either on barium or CT imaging, can assist in diagnosis. CT can also show inflammatory processes such as pancreatitis, abscesses, or ➲ retroperitoneal haemorrhage.

Management

When ileus is precipitated by laparotomy, treat with bowel rest, IV fluids, and correct electrolyte imbalances. Use opioids for pain sparingly; employ other analgesics where possible. Pass NG tube if distension or vomiting. Evaluate nutritional status (may require ➲ parenteral nutrition). Search for alternative for cause if ileus lasts >5d.

Box 4.36 Causes of ileus

- Laparotomy.
- Electrolyte disturbance: ↓ K, ↓ or ↑ Mg/Ca.
- Drugs: narcotics, phenothiazines, anticholinergics.
- Intra-abdominal inflammation: ➲ appendicitis, ➲ diverticulitis, perforated duodenal ulcer.
- Retroperitoneal inflammation: lumbar fracture, ➲ pancreatitis, ➲ retroperitoneal haemorrhage, pyelonephritis.
- Intestinal ischaemia**:** arterial embolus or thrombosis, mesenteric venous thrombosis.
- Thoracic disease: myocardial infarction, lower lobe pneumonia.
- Systemic sepsis.

Immune checkpoint inhibitor induced enterocolitis

Aetiology and pathogenesis

Immune checkpoint inhibitor therapies (e.g. ipilimumab, nivolumab, pembrolizumab) are a novel group of monoclonal antibodies with efficacy against a wide range of malignancies, including melanoma, renal cell carcinoma, non-small cell lung cancer, urothelial carcinoma, and Hodgkin lymphoma. Work through blocking receptors that normally inhibit T cells, leading to heightened T cell activity responsible for antitumoral effect. However, through the same mechanism also cause immune-related adverse events, with GI toxicity second only in frequency to dermatological toxicity.

Clinical features

- Most commonly manifests as enterocolitis reminiscent of idiopathic ➔ inflammatory bowel disease.
- GI features may include anorexia, nausea, vomiting, diarrhoea, abdominal pain, and rectal bleeding.
- Systemic features, including pyrexia and fatigue, common. Uncertain whether enterocolitis associated with systemic features is necessarily linked to more severe intestinal inflammation (as would be the case in ➔ ulcerative colitis).
- Diarrhoea associated with these drugs is normally mild or moderate; however, minority (<10%) develop severe diarrhoea or life-threatening complications (such as perforation).
- Median time to onset ~4–7wk after starting treatment, but broad range, with some patients experiencing symptoms months and even years after cessation of therapy.

Diagnosis

- Should be considered in all patients who have received immune checkpoint inhibitors presenting with gastrointestinal symptoms, even following their cessation.
- Infective causes of diarrhoea should be excluded.
- Endoscopic investigation with flexible sigmoidoscopy and biopsy should be arranged to assess for mucosal inflammation. Colonoscopy can usually be avoided but should be considered in treatment refractory or persistent diarrhoea, especially in patients with normal sigmoidoscopy.
- Histology tends to show acute colitis with neutrophilic and eosinophilic inflammatory infiltrate.

Management

- In cases of confirmed immune checkpoint inhibitor induced enterocolitis, early administration of corticosteroids is recommended with prednisolone 40mg PO for mild disease, escalating to IV corticosteroids in absence of response within 3–5d.
- In moderate-to-severe disease, methylprednisolone 1mg/kg IV should be considered.

- Patients who do not respond to high dose IV corticosteroids within 3d should be switched to → INFLIXIMAB.
- Treatment options for patients not responding to infliximab, include → VEDOLIZUMAB, → CALCINEURIN INHIBITORS, or mycophenolate mofetil.

Immunoglobulin deficiency

Primary causes

Selective IgA deficiency (serum concentration <0.07g/L) most common. Prevalence 1/ 400 in Caucasian populations (lower in Asian communities). Rarely of clinical significance. Little if any ↑ risk of infection. Associated with ➲ coeliac disease (detected in 2% of coeliac patients) and ➲ pernicious anaemia. Main risk is false-negative tests for IgA antiendomysial antibodies.[1]

Common variable immunodeficiency (CVID) involves defective B cell terminal differentiation. Presents in 2nd or 3rd decade with pneumonia or diarrhoea. Of latter, ⅔ have malabsorption due to villous atrophy, but ➲ giardiasis and ➲ bacterial overgrowth also common. Atrophic gastritis, ➲ pernicious anaemia, and ➲ coeliac disease can develop.

X-linked (Bruton's) agammaglobulinaemia is a defect of B cell maturation that abrogates functional antibodies. Presents with recurrent pyogenic infections from infancy. GI infections in 30%, usually ➲ *Campylobacter* or ➲ giardiasis. Risk of ➲ lymphoma and leukaemia increased. Treated with IVIG.[2]

Hyper-IgM syndrome caused by defective T cell CD40L, resulting in B cells unable to produce specific IgG or IgA. One-third get chronic diarrhoea. ➲ *Cryptosporidium* common, but no pathogen isolated in most cases. Risk of chronic cholangiopathy and liver cancer.

Secondary causes

Include drugs (particularly rituximab, cyclophosphamide, azathioprine, penicillamine, sulfasalazine, and phenytoin), haematological malignancies (especially myeloma), viral infections (EBV, CMV, and HIV), nephrotic syndrome, and ➲ protein-losing enteropathy.

Inflammatory bowel disease

See: ➲ Crohn's disease, ➲ Microscopic colitis, and ➲ Ulcerative colitis.

Intestinal failure

Occurs when intestinal absorption ↓ to extent that macronutrient and/or water and electrolyte supplements are needed to maintain health ± growth. Untreated, malnutrition, and dehydration result.

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[1] Yel L (2010). *J Clin Immunol* **30**: 10–16.

[2] Kobrynski LJ & Mayer L (2011). *Clin Immunol* **139**: 238–48.

Categorization

- **Type 1** Acute, short-term, and usually self-limiting condition (e.g. acute ▲ **bowel obstruction** ▲, ➔ ileus, or transient enteritis due to infection or chemotherapy).
- **Type 2** Prolonged acute condition (e.g. fistulation). Often in metabolically unstable patients, requiring complex multidisciplinary care and IV supplementation over weeks to months.
- **Type 3** Chronic condition (e.g. bowel resection resulting in ➔ short bowel syndrome, ➔ Crohn's disease, ➔ radiation enteritis, or small bowel dysmotility) requiring IV supplementation over weeks to months.

Severity

- **Mild** Oral nutritional ± fluid supplements sufficient. May also be categorized as 'intestinal insufficiency'.
- **Moderate** Enteral (e.g. NG/NJ) supplements required.
- **Severe** ➔ Parenteral nutrition necessary.
- Patients may adapt over time, such that initially severe intestinal failure can transition to mild category.[3]

Guideline

ESPEN guideline on chronic intestinal failure in adults (2016). 🖱 http://www.clinicalnutritionjournal.com/article/S0261-5614(16)00047-9/abstract.

Intestinal ischaemia

Can be acute or chronic; due to arterial or venous disease; and may affect small bowel, colon, or both. Collateral circulation to stomach, duodenum, and rectum accounts for rarity of ischaemic episodes affecting these regions. Splenic flexure and sigmoid colon most at risk. Management conservative (IV fluids, bowel rest, broad-spectrum antibiotics, and anticoagulation) if no sign of perforation or gangrene.

Acute mesenteric ischaemia

Usually arterial. Most commonly superior mesenteric artery embolus (less commonly non-occlusive mesenteric ischaemia or superior mesenteric artery thrombosis), and presents with ▲ **acute abdominal pain** ▲. Venous thrombosis causes 5–10%. Most patients with arterial thrombosis have generalized arteriosclerosis.

Colonic ischaemia (ischaemic colitis)

Most common form of intestinal ischaemia. Presents with sudden onset cramping pain in left iliac fossa (LIF), fresh or altered blood mixed with stool within 24h, and mild-to-moderate tenderness over bowel. Diagnosis made by careful colonoscopy or (perhaps better) contrast-enhanced CT. Barium studies less sensitive than colonoscopy: the classic 'thumb-printing' disappears in days as submucosal haemorrhages resorbed and overlying mucosa sloughs. More than 50% resolve on conservative management. Increasing tenderness, fever, and ileus suggest infarction and mandate urgent operative intervention.

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[3] Nightingale JM (2003). *Proc Nutr Soc* **62**: 703–10.

Intestinal angina (chronic mesenteric ischaemia)

Uncommon, causing pain due to small bowel ischaemia as gastric blood flow ↑ after meal. Classically presents with pain within 30min of eating, resolving over 1–3h. Best test is angiography, with balloon angioplasty as preferred therapy. Recurrence common but may be reduced by stenting.

Vasculitis of splanchnic circulation

➲ Polyarteritis nodosa and ➲ rheumatoid arthritis can affect medium-sized vessels, and any cause of systemic vasculitis can cause small vessel occlusion and segmental ischaemia.

Intestinal transplantation

Intestinal transplantation has evolved in recent decades from being considered an experimental procedure to what is now a preferred long-term option for patients with ➲ intestinal failure who have developed irreversible complications associated with ➲ parenteral nutrition. During this time advances in organ preservation, surgical technique, immunosuppression, and postoperative management have led to both an ↑ volume of transplants performed and improved outcomes. In many cases, patients may require liver-small bowel graft or ‘multivisceral’ graft, including other organs such as stomach and pancreas. Current UK indications for referral of adults to intestinal transplant centre are shown in Box 4.37.

Box 4.37 Indications for referral to intestinal transplant centre

Complications of parenteral nutrition

- Liver disease due to ➲ parenteral nutrition (irreversible despite management by established parenteral nutrition centre).
- Progressively compromised vascular access for parenteral feeding (loss of all but two major venous access points, at least one of which is above diaphragm).
- Recurrent or life-threatening central line sepsis (including fungal).
- Inadequate maintenance of hydration/nutrition despite ➲ parenteral nutrition.

Requirement for extensive evisceration

- Desmoid tumours.
- Trauma.
- Rare malignancies (including ➲ neuroendocrine tumours).

Guideline

BSG guideline for management of patients with a short bowel (2006).

Intramural haematoma

Rare, but can occur spontaneously, especially in patients using anticoagulant or antiplatelet drugs, and with clotting disorders. Most common in oesophagus, in patients with history of retching.

Clinical features

Include sudden onset chest pain, dysphagia, and haematemesis. Rapidity of onset can mimic MI, dissecting aneurysm, or pulmonary embolus. Small bowel intramural haematoma can present with ▲ **acute abdominal pain** ▲ and ▲ **intestinal obstruction** ▲.

Diagnosis

- Best made by contrast radiography or CT.
- Endoscopy not always necessary and should be pursued with caution as many intramural haematomas are contained perforations. No serosal layer in oesophagus, so air inflation can convert a contained into a free perforation.

Management

- Most resolve over 7–10d.
- Surgery indicated in ongoing massive haematemesis.
- Small bowel haematomas usually managed conservatively with correction of coagulation, although rarely require surgery for intestinal obstruction.

Intrinsic factor (IF)

50kDa glycoprotein secreted by parietal cells. One of two proteins that bind cobalamin (➲ vitamin B_{12}), the other being R binder protein. Most B_{12} initially binds to R binder in stomach. Complex is then cleaved by pancreatic trypsin, and freed B_{12} binds to IF. The IF–B_{12} complex binds to a specific ileal receptor called cubilin that mediates endocytosis. B_{12} is then transported to tissues bound to transcobalamin II.

Secretion of IF usually in physiological excess: most patients with hypochlorhydria produce enough to prevent B_{12} deficiency, and histamine receptor antagonists/PPIs do not induce IF deficiency. Circulating antibodies to IF are found in ➲ pernicious anaemia. Diagnosis of vitamin B_{12} deficiency due to loss of functioning IF historically clarified by Schilling test, although rarely (if ever) performed today.

Intussusception

Invagination of a proximal segment of bowel into adjacent distal segment (Fig. 4.13). Common cause of small bowel obstruction in children, and 5% of cases in adults. Important point is that in adults intussusception that presents clinically always needs investigating since there is usually a pathological cause, for example tumours (e.g. ileocaecal ➔ carcinoid), inflammatory lesions, ➔ Meckel's diverticulum. Interestingly, asymptomatic transient intussusception is occasionally noted as an incidental finding on cross-sectional abdominal imaging.

Clinical features

Usual presentation is with partial small bowel obstruction. Occult or overt rectal bleeding may occur.

Diagnosis

Demonstrated by US or CT.

Management

Usually managed conservatively (if underlying pathology excluded). Otherwise, surgical reduction/resection.

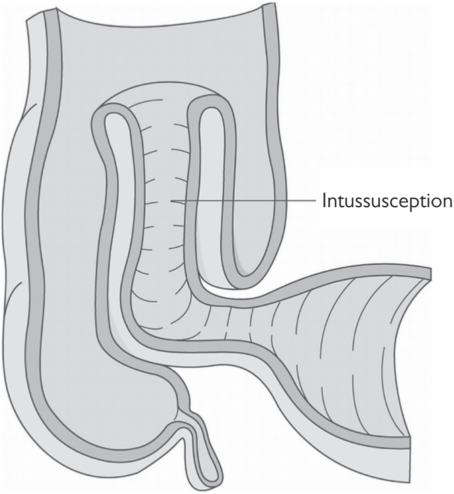

Fig. 4.13 Intussusception.

Iron

Dietary iron comprises haem iron (meat, fish, poultry) and non-haem iron (vegetables, grains, and fruits). Poor intake alone rarely causes anaemia, but may deplete stores and combines with any cause of malabsorption or blood loss to produce anaemia. Absorption and losses are ≈1mg/d in adults; menstrual loss in women 5–50mg/mo.

Absorption

Takes place in duodenum and proximal small bowel. Absorption ↑ by ➲ vitamin C by maintaining iron in ferrous state, and ↓ in cases of reduced acid secretion (atrophic gastritis, gastric surgery, prolonged antacid treatment) and small bowel disease (e.g. ➲ coeliac disease). Elevated in ➲ haemochromatosis, and can ↑ 2–3-fold to compensate for increased loss.

➲ **Hepcidin** is a key regulator of absorption, inhibiting transport by binding to iron export channel ferroportin (on basolateral enterocyte cell membrane, and macrophages). Results in accumulation of iron within cells. In GI tract, this prevents iron transport into portal system, reducing systemic absorption. ↑ Hepcidin activity in chronic inflammation and consequent iron sequestration within macrophages partially responsible for anaemia of chronic disease.[4]

Iron deficiency

Common (5–10% of pre-menopausal ♀, 1–5% of ♂). In groups other than premenopausal ♀, assumption is usually of chronic occult GI bleeding and this underlies routine search for GI pathology. 12% of premenopausal ♀ with iron-deficiency anaemia have significant GI abnormalities, so investigation in this group is also important.

Diagnosis

- Haemoglobin, iron/TIBC, ferritin, and transferrin saturation required for accurate diagnosis. Diagnostic criteria depend on the degree of inflammation. TIBC usually ↑.
- In patients without biochemical or clinical evidence of inflammation, appropriate criteria are serum ferritin <30ng/L or transferrin saturation <16%.
- In presence of inflammation, lower limit of ferritin consistent with normal iron stores is 100ng/L.

Finding the cause

Overall, upper GI lesions twice as common as colonic (40% compared with 20% in several large series). Trivial lesions such as mild gastritis and small adenomas do not contribute to iron deficiency, although ➲ *Helicobacter pylori*-associated gastritis as well as large ➲ hiatus hernias, gastric achlorhydria, and gastric atrophy have been implicated. Right-sided ➲ colon cancers are classic occult colonic source of bleeding; ➲ angiodysplasia and adenomas are nearly as frequent.

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[4] Lopez A *et al* (2016). *Lancet* **387**: 907–16.

Investigations

- Symptoms are not a reliable guide.
- All patients should be screened for serological evidence of ➔ coeliac disease.
- Investigation should include upper GI endoscopy and low duodenal biopsy, and colonoscopy (particularly in those >50y). Pre-menopausal women should be investigated in presence of other symptoms or significant family history of GI pathology.
- May be a role for ➢ enteroscopy, ➢ video capsule endoscopy, and occasionally ➢ angiography or labelled ➢ red cell scan in cases where iron deficiency persists and initial endoscopies negative.
- Do not forget to consider urinary blood loss in any differential.

Treatment

Oral iron

- Traditional advice is to administer elemental oral iron 100–200mg/d alongside vitamin C, which improves absorption. Elemental iron concentration various between preparations (Table 4.23).
- Some evidence that alternative strategy, administering low dose iron (40–80mg), on alternate days, may be more effective, due to compensatory rise in hepcidin induced by regular higher dose iron.[5]
- Continue treatment for 3mo to replenish stores. In general, differences in tolerability due to differences in iron concentration.
- Prophylactic iron may be appropriate in malabsorption, pregnancy, and post-gastrectomy.

Table 4.23 Elemental iron content of common oral iron preparations.

Preparation	Formulation	Elemental iron
Ferrous sulphate	200mg tablet	65mg
Ferrous gluconate	300mg tablet	35mg
Ferrous fumarate	210mg tablet	68mg

Parenteral iron

Traditionally reserved for patients who cannot tolerate or absorb oral iron. Recent guidelines suggest IV iron is preferred route of administration in ➔ inflammatory bowel disease. Various formulations available, although high molecular weight iron dextran obsolete because of the potential for severe anaphylactic reaction. Iron sucrose (Venofer®) widely used in UK, but several infusions required; allergic reactions may occur so 1st dose should be closely monitored. Total dose iron infusion possible using low molecular weight iron dextran (Cosmofer®) or iron carboxymaltose (Ferrinject®).

Guideline

🖱 BSG guideline for management of iron-deficiency anaemia (2011).

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[5] Moretti D *et al* (2015). *Blood* **126**: 1981–9.

Irritable bowel syndrome (IBS)

Common chronic illness (estimated 10% of global population), characterized by abdominal discomfort and disturbed bowel habit. See Box 4.38 for diagnostic criteria.

Epidemiology

Found all over world but different cultures have varying perceptions of disease and illness-seeking behaviour. In West, more common in ♀ and those aged <50y.

Clinical features

- Typical features shown in Box 4.39.
- Patients experience different predominant (≥25% of bowel movements) stool patterns, including constipation (IBS-C), diarrhoea (IBS-D), or mixed pattern (IBS-M). Recognition of the subtype plays an important role in selection of diagnostic tests and treatment.

Box 4.38 Rome IV criteria for irritable bowel syndrome

Recurrent abdominal pain on average at least 1d/wk in last 3mo associated with 2 or more of the following features:

- Related to defaecation.
- Associated with change in stool frequency.
- Associated with change in form (consistency) of stool.
- Symptoms must have started at least 6mo ago.

Symptoms supporting diagnosis of IBS:

- Abnormal stool frequency.
- Abnormal stool form.
- Difficulties in evacuation.
- Passage of mucus.
- Bloating or feelings of distension.

Box 4.39 Clinical features supporting the diagnosis of IBS

- Rome IV criteria.
- Long history with relapsing and remitting course.
- Exacerbations triggered by life events.
- Coexistence of anxiety and depression.
- Associated with symptoms in other organ systems.
- Symptoms aggravated by eating.

Pathophysiology

Motility

Intestinal contractile and electrical activity ↑ but probably exaggerated response to stimuli rather than physical pathology. There is ↑ sensitivity to visceral stimulation, although wide variations in subgroups of IBS patients with diarrhoea or constipation.

Triggers for sensitization

Currently much interest in the role of inflammation and alterations in gut microflora. Proliferation of intestinal mast cells and sympathetic afferent excitation via ↑ neuropeptide release have been proposed as mechanisms by which food or stress may trigger symptoms. Association between emotion and gut motility, which has been considered as further factor.

Post-infective sensitization

Post-infective IBS associated with bacterial, protozoan, helminth, and viral infections. Mechanisms largely undefined, but three possible theories: bile salt malabsorption, increased enteroendocrine cells, and altered gut microflora due to antibiotic use.

Food intolerance

- Studies of dietary restriction followed by re-introduction suggest ➔ food intolerance in 30–60% of IBS patients; however, immunological and biochemical correlations lacking.
- Despite reported association with atopy, skin testing with food-derived allergens of dubious relevance.
- Evidence that eliminating specific foods in patients with IBS who have elevated IgG levels associated with those foods may ↓ symptoms,[6] but currently no role for IgG testing in diagnosis of food intolerance or allergy.
- Another theory suggests symptoms may relate to impaired absorption of carbohydrates: fermentable oligo-, di-, and monosaccharides and polyols (➔ FODMAPs) fermented in distal small bowel and colon, giving rise to symptoms and ↑ intestinal permeability. Fructose, lactose, and gluten sensitivity have also been reported in IBS.

Diagnosis

- IBS not diagnosis of exclusion. Based on Rome criteria (Box 4.38).
- Decision to investigate based on patient age, family history, and presence of 'alarm' symptoms (Boxes 4.40 and 4.41).
- Evidence of anaemia or iron deficiency should prompt additional investigations.
- Patients with potential IBS-D should have measurement of CRP, ▷ faecal calprotectin, and screening for ➔ coeliac disease.

Treatment

Successful management combines individualizing treatment of predominant symptoms and conferring insight on how symptoms may relate to emotional stresses. Time spent in exploring association between symptoms and life events often pays dividends. A trusting patient-physician relationship is key to management, with focus on 'helping' rather than 'curing'.

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[6] Atkinson W *et al* (2004). *Gut* **53**: 1459–64.

Box 4.40 Clinical features suggesting organic disease other than IBS

- Onset after age 50.
- Progressive deterioration.
- Fever.
- Weight loss.
- Rectal bleeding (not caused by fissures or haemorrhoids).
- Unexplained iron deficiency.
- Nocturnal diarrhoea.
- Steatorrhoea.
- Dehydration.

Box 4.41 Investigations in suspected IBS

- Routine haematology/biochemistry and sigmoidoscopy with rectal biopsy (if diarrhoea) are reasonable starting investigations.
- If diarrhoea persistent, serum B_{12}, folic acid, iron studies, thyroid function, coeliac antibodies, liver function tests, and stool microscopy should be done.
- Faecal calprotectin in suspected IBS-D (↑ points against IBS).
- In suspected IBS-D consider colonoscopy to exclude ➲ microscopic colitis, and if high faecal calprotectin.
- Faecal urgency or incontinence suggests need for anorectal manometry (see ➤ p. 157).

Lifestyle measures

Exercise

Although physically active individuals open bowels more frequently than sedentary patients, structured exercise appears to improve IBS symptom control. Recommend at least 20min walking each day.[7]

Diet

- **General advice** Have regular meals, and take time to eat. Drink at least 8 cups of fluid/d, especially water or other non-caffeinated drinks. Restrict tea and coffee to maximum 3 cups/d, and ↓ intake of alcohol and fizzy drinks. May help to limit intake of high fibre food.
- **Exclusion diets** Patients often believe ➲ food intolerance contributes to symptoms and some sufferers benefit from eliminating certain foods from diet. Detection of intolerance is often difficult even with the help of food diaries and dieticians. Many studies rely on exclusion diets that are labour-intensive and time-consuming. Depend on the principle of stabilizing patient on very bland diet for few days then gradually introducing one or two favourite foods/day. About 30% of patients can identify precipitating food using this approach. In the past, attempts to test for food intolerance focused on classic food allergy based on IgE-mediated antibody responses, although immediate type 1 hypersensitivity is rare in IBS.

[7] Johannesson E *et al* (2011). *Am J Gastroenterol* **106**: 915–22.

- **Gluten exclusion** Evidence conflicting. Although some studies supportive, likely that widespread negative media reports about gluten have ↑ probability of nocebo effect.
- ➔ **FODMAPs** These carbohydrates lead to ↑ small intestinal and colonic water secretion and fermentation, which ↑ production of ➔ short-chain fatty acids and gas. Low FODMAP diet suggested to improve symptoms in IBS, though long-term efficacy data awaited.

Prebiotics and probiotics

Although meta-analysis does suggest benefit,[8] the variety of preparations included means that the currently available data do not allow clear recommendations to be made.

Biofeedback

See ➔ biofeedback. Effective in IBS patients (particularly IBS-C) with dyssynergic defaecation.

Pharmacological therapies

Evidence for efficacy of therapies is complicated by high placebo rates with all modes of treatment. This may relate to benefits observed with alternative or complementary remedies (Box 4.42).

Drugs useful in managing IBS are shown in Box 4.43. Sometimes drugs useful for one symptom can make another worse. In particular, dietary fibre or stimulant laxatives can make bloating and abdominal pain worse. We recommend use of non-stimulant osmotic laxatives such as macrogols for constipation. Antidepressants used in low doses have visceral analgesic effect that should be explained to patient as this often facilitates acceptability. Tricyclics can have supplemental benefit in relieving insomnia.

Newer drugs aim to modifying visceral sensitivity and reactivity by using ligands for intestinal serotonin receptors. Long-term benefits of this approach remain to be determined.

Box 4.42 Complementary and alternative therapies in IBS

Evidence accumulating that variety of complementary and alternative therapies can modulate stress hormones and other physiological functions, although difficult to actively encourage uptake of any modality on basis of current evidence. Different therapies directed at different aspects of healing:

- Physical therapies (massage, acupuncture, reflexology, shiatsu) may work on release of tension.
- Meditation and hypnotherapy produce focused relaxation that may facilitate cognitive behavioural change.
- Biofeedback may help patients gain control over their symptoms.

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[8] Ford AC *et al* (2014). *Am J Gastroenterol* **107** (**suppl 1**): S2–6.

Box 4.43 Drugs useful in managing IBS

Target agents according to symptoms.

- Antispasmodics for abdominal pain: mebeverine, hyoscine butylbromide, modified release peppermint oil capsules, alverine citrate.
- Antidiarrhoeal agents: → LOPERAMIDE, → COLESTYRAMINE.
- Anticonstipating agents: macrogols.
- Antidepressants: tricyclics, SSRIs.
- Pro-secretory agents (for IBD-C):
  - Linaclotide. Guanylate cyclase-C agonist that ↑ intestinal Cl^- secretion and ↓ firing of visceral afferent pain fibres. Dose of 290μg od 30–60min prior to breakfast improves constipation, abdominal pain, and bloating, usually without causing limiting diarrhoea.
  - Lubiprostone. Cl^- channel activator. Stimulates intestinal fluid secretion and improves IBS-C symptoms at dose of 24μg bd.
- → 5-HT_4 receptor agonists. Prucalopride 2mg od improves colonic transit time, bowel frequency, and quality of life in trials. Approved for treatment of chronic constipation, although not IBS specifically. The authors' usual practice is to start at 1mg od then ↑ to 2mg od if tolerated, and review at 12mo.
- Antibiotics: → RIFAXIMIN 550mg tds improves symptoms in short-term,[9] although clinical experience suggests many responders eventually develop recurrent symptoms. Concern with other antibiotics about development of antimicrobial resistance.

Prognosis

High probability of remaining free of severe symptoms, but symptoms usually persist for long time (only 5% symptom-free 5y). Medical intervention relieves or improves symptoms and quality of life in ≈⅔. Outcome best in ♂ with short history, IBS-C, and if good initial response to treatment. Long-term response best where psychosocial issues explored and patient education emphasized (Box 4.44).

Box 4.44 IBS: all in the mind?

- IBS is more common in those attending psychiatric clinics, and associated with psychological factors including anxiety and depression. Only prospective data come from IBS triggered by episode of gastroenteritis: psychological factors at onset of infection appear to predict development of chronic bowel symptoms.
- IBS patients appear to show particular illness behaviours. They consult doctors more frequently about minor ailments, and overlap with chronic fatigue syndrome and fibromyalgia.
- IBS patients report more stressful life events, ranging from loss to familial disruption, domestic or career dissatisfaction, or abuse (physical or sexual). Loss of self-esteem and autonomy frequently manifest in somatic symptoms, including those of IBS.

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[9] Menees S *et al* (2012). *Am J Gastroenterol* **107**: 28–35.

Guidelines

🖱 NICE guideline on irritable bowel syndrome (2015).

🖱 British Dietetic Association systematic review and guidelines for dietary management of irritable bowel syndrome (2016).

🖱 British Dietetic Association systematic review and guidelines for use of probiotics in irritable bowel syndrome (2016).

Islet cell tumours

See: ➔ Pancreatic endocrine tumours.

Isospora

See: ➔ Coccidia.

Section 4

J

Jaundice: see ► Approach to recent-onset jaundice *432*
Jejunal diverticulum *432*
Juvenile polyps and polyposis *432*

Jaundice

See: ► Approach to recent-onset jaundice.

Jejunal diverticulum

Jejunal diverticula 5× less common than duodenal. Reported in 0.5–7% of small bowel series, and 0.3–1.3% at autopsy. Prevalence in line with ➔ Meckel's diverticula. Can be associated with connective tissue disorders such as ➔ systemic sclerosis, ➔ systemic lupus erythematosus, ➔ Ehlers–Danlos syndrome, and ➔ amyloidosis. Most cases asymptomatic, but can cause pain, bleeding, diarrhoea, and fever. Malabsorption can arise from stasis and ➔ bacterial overgrowth. Diagnosis most efficient with barium contrast radiograph but can also be seen on CT and MRI. Treatment surgical for significant bleeding or diverticulitis. Malabsorption treated with oral antibiotic (e.g. tetracycline 250mg PO qds for 7–10d) to limit bacterial overgrowth.

Juvenile polyps and polyposis

Juvenile polyps are mucosal tumours consisting of excess lamina propria and dilated cystic glands rather than epithelial cells. They are hamartomas and appear to be acquired, being most common in age group 1–7y. Usually regress spontaneously but can occur in adults. Typically single, range in size from 3mm to 2cm, and most common in rectum. May prolapse during defaecation. Although no malignant potential when single, removal suggested because of tendency to bleed. Rarely associated with proximal adenomas.

Juvenile polyposis syndrome

Defined by ≥10 juvenile polyps, juvenile polyps occurring throughout GI tract, or any number of juvenile polyps with family history of juvenile polyposis. Associated with germline mutations in *PTEN* and *DPC4*, which are tumour suppressor genes (DPC4 has role in signalling through TGF-β).[1] When polyps are multiple, ↑ cancer risk because of adenomatous tissue present in some polyps, rather than the juvenile polyps *per se*.

If colonoscopy reveals polyps, upper GI endoscopy should be carried out. Lifetime cancer risk 1 in 3. No formal screening or surveillance guidelines exist but following intervals recommended:

- Colonoscopy every 2y for patients with juvenile polyposis
- 3-yearly screening, beginning at age 12, for 1st-degree relatives.

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[1] Jung I *et al.* (2015). *World J Gastrointest Oncol* **7**: 347–55.

Section 4

K

Kaposi’s sarcoma *434*

Kaposi's sarcoma

Moritz Kaposi was a Hungarian dermatologist who, in 1872, described 5 patients with aggressive multiple pigmented cutaneous sarcomas. Kaposi's sarcoma (KS) is caused by human herpes virus-8 (HHV-8/KSHV). Histogenesis likely of lymphatic endothelial cell origin. Untreated, lesions progress from purple-red to brown patches (extravasated RBCs degrade to haemosiderin), to plaques then nodules. Four subtypes: ***classic*** (elderly Mediterranean men, cutaneous); ***endemic*** (non-HIV-infected African patients, lymphadenopathy); ***epidemic*** (HIV-infected patients, AIDS-defining though incidence markedly decreased with HAART such that one-third now present in patients on successful therapy with undetectable VL and near-normal CD4 counts); and ***immunosuppression-associated*** (solid organ transplants).

GI involvement

Common in HIV and immunosuppression-associated subtypes. Often asymptomatic but marker of poor prognosis. Risk increased if CD4 <100 cells/μl, VL ≥10,000 copies/ml or MSM. Any part of GI tract may be affected but oral cavity common (35%), causing pain, bleeding, trismus, or dysphagia. Palatal KS predicts endoluminal tumours.

KS more frequent in small than large bowel. Usually presents with haemorrhage, but can cause obstruction, intussusception, perforation, or protein-losing enteropathy. Lesions typically small but can bleed torrentially. Best diagnosed endoscopically though small bowel lesions may require capsule endoscopy or CT angiography. Macroscopically resemble cutaneous lesions. Histology: submucosal vascular spindle-shaped cells, neovascularization with ectatic vessels, and extravasated RBCs. Immunostaining positive for HHV-8, CD31, and CD34. Hepatic KS previously common on post-mortem but now unusual. Tumours rarely clinically apparent, but can be diagnosed via CT and biopsy.

Treatment

For single lesions, excision, intralesional vinblastine, topical alitretinoin, electrochemotherapy, or cryotherapy are curative options. For multiple lesions in a limited area, radiotherapy effective (although causes severe mucositis if used for oral KS). Extensive/recurrent disease managed with chemotherapy (liposomal anthracycline 1st line; paclitaxel or oral etoposide 2nd line) and radiotherapy. Interferon alfa effective but significant toxicity. Drugs targeting HHV-8 (ganciclovir and foscarnet) are unproven.[1] In HIV-associated disease, HAART often results in lesion regression, although may flare as part of IRIS; as response unpredictable, systemic therapy ± local radiotherapy often instituted simultaneously in higher grade/disseminated disease. In transplant recipients, calcineurin inhibitor withdrawal, or switching to sirolimus, is often sufficient; if this fails, surgery ± chemoradiotherapy are required.

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[1] Sgadari C *et al.* (2011). *Expert Opin Pharmacother* **12**: 1669–90.

Section 4

L

Lactose intolerance *436*
Laxative abuse: see also → LAXATIVES *436*
Leiomyomas: see ➔ GIST (gastrointestinal stromal tumours) *436*
Leptospirosis *437*
Lichen planus *438*
Listeria *439*
Lithotripsy *439*
Liver abscess *440*
Liver biopsy (LBx): see ▶ 'Liver biopsy' (p. 178) *441*
Liver function tests (LFTs): see ▶ 'Liver function tests' (p. 146) *441*
Liver support devices *441*
Liver transplantation *442*
Los Angeles grading: see ➔ Oesophagitis *445*
Lymphangiectasia *446*
Lymphomas in GI tract *446*

Lactose intolerance

- Deficiency of brush border lactase can lead to lactose intolerance. Symptoms are bloating, cramps, wind and diarrhoea after milk or dairy ingestion (although milk protein allergy or fat intolerance are alternative causes).
- Most common cause is acquired lactase deficiency. This is regulated at the gene transcriptional level and varies in different populations. Incidence ~10% in people of north-western European origin, 40% in Mediterranean, 60% in Asian, and 90% in Chinese individuals.
- Even in populations where lactase activity persists, levels are lower than other disaccharidases, making lactose digestion more susceptible to impairment by acute GI infections where brush border lost.
- In cases of suspected lactose intolerance, simple screening test is to ask patients to undertake 'milk challenge', consisting of 1 pint of skimmed milk (~25g lactose):
  - If no symptoms result, then intolerance unlikely.[1]
  - If this causes recurrence of symptoms, diagnosis should be confirmed using lactose hydrogen ▹ breath test (see p. 152).
- Treatment consists of either lactose-free diet or lactase supplements.

Laxative abuse (See also → LAXATIVES)

Patients may abuse laxatives for variety of reasons (see also ► Approach to eating disorders, ➲ bulimia). Detection depends on high level of suspicion. Hypokalaemia may complicate purgative abuse.

- Melanosis coli suggests ingestion of anthracene laxatives. Concern that chronic use may impair colonic motility, though this is disputed.
- Faecal osmolality <290mOsm/kg suggests stool dilution with water.
- High faecal osmotic gap may suggest magnesium ingestion. Calculate as 290-2*[stool Na^+ + stool K^+]. Normal range is 50–100mOsm/kg).
- Mixing stool with hypertonic urine gives very high faecal osmolality, with negative faecal osmotic gap because of high urinary concentrations of Na^+ and K^+.
- For additional details on management, see ► Approaches to eating disorders and ➲ bulimia.

Leiomyomas

See: ➲ GIST (gastrointestinal stromal tumours).

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[1] Spiller R *et al*. (2007). *Gut* **56**: 1770–98.

Leptospirosis

Background

- Spirochaete. Endemic in tropics (where conditions for transmission favourable; 30% seropositive for exposure). In the West, *Leptospira icterohaemorrhagiae* mainly carried by rats; ≈60 confirmed cases/y in UK, of which 25% acquired abroad.[2] Direct contact with organism in soil, water, or urine (enters through skin abrasions/cuts) explains epidemiological link with sewage workers and farmhands. ♂:♀ ratio 9:1, reflecting risk factor exposure.
- Weil's disease refers to the 10% of infections that result in clinical liver disease.

Clinical features

- Incubation 7–12d, followed by biphasic illness.[3]
- Initial septicaemic phase with influenza-like illness: fever, rigors, headache (often retro-orbital), severe myalgia, dyspnoea. Lasts 4–7d. Improves with clearance of circulating *Leptospira*.
- Second immune-mediated phase occurs within 2d of 1st phase finishing, characterized by:
  - Fever.
  - Conjunctival suffusion, iritis.
  - Skin lesions (petechiae, purpura, or ecchymosis).
  - Meningeal irritation (CSF may show lymphocytic pleocytosis).
  - Jaundice (principally cholestasis, rather than hepatocellular).
  - ECG changes (in 50%): particularly pericarditic changes or 1st degree heart block; T wave inversion can occur.
  - Rhabdomyolysis. Usually mild.
  - Renal failure with acute tubular necrosis. Oliguria is a significant predictor of mortality.
  - Pulmonary haemorrhage and ARDS.
- Death (5–10%) due to renal/respiratory disease (rarely liver failure).

Investigations

❗ Diagnosis never made unless thought about! Careful history of possible exposure essential (e.g. caving, 'outward bound' course). Consider in jaundiced patients with bilirubin disproportionately ↑ compared to ALT/AST or with ↑ CK) See ► Approach to recent-onset jaundice.

- FBC: ↓ Hb, ↑ WCC, ↓ platelets.
- LFTs: ↑↑ Bn, ↑ AST, ALP normal. ↑ PT/APTT in severe disease.
- Creatine kinase elevated in >50% with liver disease.
- Blood ± CSF culture (± PCR). High yield in 1st phase (wk 1). Leptospira replicate slowly, so can only be reported as truly negative after 6–8wk. PCR-based tests more sensitive, and positive earlier.[4]
- Urine (dark field) microscopy positive in 2nd phase (wk 2 and 3).
- ELISA for *Leptospira* IgM highly sensitive and specific, and most widely used diagnostic test. Positive result confirmed by antigen testing (microscopic agglutination test; MAT).

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[2] Forbes AE *et al*. (2012). *QJM* **105**: 1151–62.

[3] Haake DA & Levett PN (2015). *Curr Top Microbiol Infect* **387**: 65–97.

Management

- Effective supportive care essential. May need dialysis.
- Insufficient evidence for corticosteroids, despite immune-mediated pathogenesis of 2nd phase.
- Antibiotic therapy (see Controversy):
    - Mild disease/prophylaxis: doxycycline 100mg bd PO for 1wk.
    - Severe disease: IV penicillin 1.5 million units qds or ceftriaxone 1g od for 1wk.
    - Risk of Jarisch–Herxheimer reaction: fever, tachycardia, and hypotension. Management supportive.

Controversy. Antibiotics for leptospirosis

Role of antibiotics remains debated as most cases resolve spontaneously. Recent Cochrane review found insufficient evidence to provide clear guidelines, but most experts would not withhold antimicrobial therapy. Some evidence disease duration shortened if initiated within 4d of onset.

Lichen planus (see Plate 6)

Pathogenesis

Chronic mucocutaneous inflammatory disease, in which cytotoxic T cells trigger apoptosis of epithelial basal cells.

Clinical features

- Usually occurs in middle age, affecting ♀>♂.
- Lesions papular, with characteristic lacy white lines on surface (Wickham's striae, caused by hyperkeratinized epithelium).
    - Cutaneous lesions typically purple, polygonal, intensely pruritic, and demonstrate Koebner phenomenon.
    - Oral disease often symmetric, white or grey, reticular, and relatively asymptomatic.
    - Oesophageal involvement occurs rarely, presenting with dysphagia or odynophagia. Lesions typically proximal and spare gastro-oesophageal junction.[4,5]
- Associations with ➔ hepatitis C, autoimmune disease, and dental treatment.
- Some drugs (NSAIDs, β-blockers, ACE inhibitors, sulfonylureas and antimalarials) can cause lichenoid reactions.
- Risk of transformation to squamous cell cancer in 1–2%.

Investigation

- Diagnosis usually clinical.
- Request hepatitis C serology unless infection already identified.
- Biopsy if diagnosis uncertain, or lesions persist despite treatment. Histology shows basal cell liquefactive degeneration with dense lymphocytic infiltrates, hyperkeratinization, and Civatte bodies.

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[4] Musso D & La Scola B (2013). *J Microbiol Immunol Infect* **46**: 245–52.

[5] Fox LP *et al*. (2011). *J Am Acad Dermatol* **65**: 175–83.

Management

- Reticular oral lichen planus can often be managed expectantly.
- If symptomatic or erosive disease, topical steroids, calcineurin inhibitors, retinoids, or photodynamic therapy effective (🖱 Cochrane review 2011).[6]
- Surgery typically reserved for high-risk dysplastic lesions.

Listeria

Gram-positive bacillus, which can cause outbreaks of gastroenteritis. Likely under-recognized.[7] Sources include raw or unpasteurized dairy products, and pre-packaged meats. Incubation highly variable (1–30d). Immunocompetent individuals develop watery diarrhoea with associated fever, headache, and nausea. Typically self-limiting, lasting ≤3d. Secondary bacteraemia unusual.

In contrast, listeriosis is a systemic disease that can affect immunocompromised patients, older adults, and pregnant women. Often associated with bacteraemia that can seed to heart valves or meninges. Treat with high-dose penicillin (e.g. ampicillin 2g IV tds), for minimum of 2wk.

Lithotripsy

In gastroenterology, lithotripsy (breaking up of stones) usually applies to bile or pancreatic duct stones. Approaches may be:

- **ERCP + mechanical lithotripsy** Where bile duct stones are too large (e.g. >15mm) to be safely removed with extraction balloon or basket, mechanical lithotripter may be required. Consists of extraction basket, over which metal sheath passed, crushing stone within duct. Smaller stone fragments then removed with balloon.
- **ERCP with cholangioscopy + laser/electrohydraulic lithotripsy (EHL).** In 10% of cases, bile duct stones cannot be removed with conventional ERCP or mechanical lithotripsy. Recent advances in cholangioscopy allow direct visualization of intraductal stones, which may be broken up with laser or EHL. Allows stone clearance in 90% of cases in which previous attempts have failed.
- **Extracorporeal shock wave lithotripsy (ESWL).** Utilizes US shock waves to fragment stones. Very limited role for bile duct stones given effectiveness of ERCP ± cholangioscopy. Has occasional role in management of painful chronic pancreatitis with obstructing stone in head of pancreas (where surgery or ERCP alone unsuccessful/precluded). No real role in management of gallbladder stones (should be managed by ➢ cholecystectomy if symptomatic).

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[6] Davari P *et al*. (2014). *Am J Clin Dermatol* **15**: 181–95.

[7] Aboutaleb N *et al*. (2014). *Curr Opin Gastroenterol* **30**: 106–15.

Liver abscess

Aetiology

In pre-antibiotic era, most pyogenic liver abscesses arose following ➲ appendicitis. May develop in pre-existing liver lesions, including ➲ hepatocellular carcinoma, especially if prior instrumentation or significant tumour necrosis (e.g. following chemo-embolization or radiofrequency ablation). Infection can also ascend from biliary tract in association with ➲ cholangitis, ➲ choledocholithiasis, ➲ *Clonorchis* infection, or ERCP. Intra-abdominal disease (e.g. ➲ colon cancer, ➲ diverticular disease) may give rise to portal bacteraemia and liver abscess.

Infections are usually polymicrobial, involving gut-derived Gram-negative (e.g. *E. coli, Klebsiella*), Gram-positive (e.g. *Enterococci, Streptococcus milleri*) and anaerobic (e.g. *Bacteroides* spp) organisms. Rarer causes include ➲ hydatid disease, ➲ TB, ➲ *Candida albicans*, and ➲ actinomycosis. *Entamoeba histolytica* is an important cause in developing countries (see ➲ amoebiasis). ➲ Portal vein thrombosis (PVT) can be associated with local/systemic infection, and portal pyaemia.

❗ Pitfall

Vital to exclude liver abscess in patients with ➲ cholangitis who remain septic despite relief of biliary obstruction.

Clinical features

- Significant variability in severity and duration of symptoms. May present acutely with RUQ pain, high fever, and septic shock, or more indolently (>1mo) with pyrexia of unknown origin (PUO), malaise, anorexia, weight loss, and dull abdominal discomfort.
- May develop tender hepatomegaly, and occasionally jaundice.

Investigation

- Bloods. Mildly abnormal LFTs (often ↑ ALP/GGT), even in absence of large duct obstruction. ↑ WCC (neutrophilia), ESR, and CRP.
- Blood cultures positive in 50–80%.
- Imaging. Abscesses may be single or multiple. US 1st modality, and highly specific. Contrast CT nearly 100% sensitive, often showing hypodense lesion with 'rim enhancement'. Vital to exclude biliary obstruction. Differential diagnoses include amoebic liver abscess (➲ amoebiasis), ➲ hydatid disease, simple cyst, and necrotic tumour.
- Abscess aspiration needed if blood cultures negative and fail to respond to initial treatment. Organism isolated in 90% if abscess aspirated prior to antibiotics.
- Look hard for reason for liver abscess (e.g. colonoscopy to exclude ➲ colon cancer in *Streptococcus milleri* abscess).

Management

- If abscess associated with biliary obstruction, biliary drainage (preferably by ERCP) is essential.
- Antibiotics should be tailored to culture sensitivities but, until available, broad-spectrum empirical cover is appropriate (e.g. 3rd generation → CEPHALOSPORIN and → METRONIDAZOLE, or piperacillin-tazobactam). Be guided by microbiologists. Antibiotics usually given for 2wk IV, and further 6wk orally. May take weeks/months for resolution; be guided primarily by clinical progress not radiological change.
- Percutaneous aspiration recommended for lesions <5cm, and percutaneous catheter drainage if >5cm.
- Surgery rarely required but should be considered with multiple, loculated abscesses.

Liver biopsy (LBx)

See: ⊳ 'Liver biopsy', p. 178.

Liver function tests (LFTs)

See: ⊳ 'Liver function tests', p. 146.

Liver support devices

- ➲ Liver transplantation as the only definitive therapeutic option for end-stage liver failure is unsatisfactory for many reasons (lack of donors; life-long immunosuppression; ethical issues).
- Artificial liver support systems remain the 'holy grail' in hepatology. Could have particular role as 'bridge' to transplant in those with ▲ **acute liver failure** ▲ awaiting donor liver, and to allow time for spontaneous recovery of native liver (e.g. post ➲ paracetamol overdose).
- Two broad types of device:
  - **Non-biological** devices aim to detoxify patient through dialysis-derived techniques. Based on principle of albumin dialysis, plasma separation, and filtration. Remove albumin-bound and water-soluble substances without having any synthetic function. The Molecular Adsorbent Recirculating System (MARS) is an extracorporeal device attached to a conventional haemodialysis machine. Patient blood circulates through special hollow-fibre filter with membrane, through which protein (albumin)-bound toxins pass and re-attach to albumin in dialysate compartment. Dialysate albumin then cleaned of toxins by continuous passage over charcoal and anion exchange resin columns, then recirculated. MARS reduces hyperbilirubinaemia and may improve ▲ **hepatic encephalopathy** ▲ and intractable pruritus. Prometheus® is a similar device that provides plasmapheresis or filtration of native albumin followed by adsorption. Recent

  randomized studies have shown no overall survival benefit for either system compared with standard care in acute-on-chronic liver failure, but benefit may be seen in type 1 ➔ hepatorenal syndrome and for those with Model for End-stage Liver Disease (MELD) score >30 (see ➔ liver transplantation).
  - **Biological** These devices employ isolated liver cells, often in conjunction with charcoal and resin columns, to replace hepatic synthetic function. Advantage of providing some synthetic activity and toxin clearance comparable with native liver. In a trial of a commercial system, overall 30d survival was not improved, although possible benefits in small subgroups. Devices appear safe, but more expensive than non-biological systems and not as extensively studied.
- Other methods of liver support under development include hepatocyte transplant, stem cell transplant, and transgenic xenografts.

Liver transplantation

Background

- Management of chronic liver disease has been transformed by cadaveric orthotopic liver transplantation (OLT). Patients are listed according to their blood group.
- Living-related liver transplantation (LRLT) results in comparable recipient survival rates, but issues remain concerning ethics, means of selection, and donor complications (0.5% donor mortality).
- Alternatives to human livers for transplant (e.g. xenotransplantation from other mammals such as pigs, or large-scale production of functioning hepatocytes) remain elusive (see ➔ liver support devices).
- End-stage liver disease due to cirrhosis accounts for ≈55% of OLT, malignancy ≈15% (see ➔ hepatocellular carcinoma), ▲ **Acute liver failure** ▲ 5–10%, and cholestasis 10% (e.g. ➔ primary biliary cholangitis, ➔ primary sclerosing cholangitis). In UK, OLT for ➔ paracetamol overdose is falling (probably due to drug supply restrictions), but proportion for ➔ hepatitis C has risen (>25%).
- Overall patient survival post-OLT >90% at 1y, and 70% at 5y.

Box 4.45 When to refer for OLT consideration?

Not an exact science, but simple answer is 'sooner rather than later'. Liver units do not want to first hear of patient with acute liver failure when in grade III ▲ **hepatic encephalopathy** ▲, or of decompensated cirrhotics by time they have become cachectic. Broadly, consider OLT when anticipated survival <2y, and where expect >50% probability of survival with good quality of life 5y after surgery. Contraindications to liver transplantation are listed in Box 4.46.

Acute liver failure (see ▲ **Acute liver failure** ▲ *and Table 4.24)*

Progression of liver synthetic dysfunction determines timing/need for OLT. PT/ INR ideal marker of this and ∴ do not correct ↑ PT/INR (e.g. with FFP) unless actively bleeding (and preferably following discussion with transplant centre).

Indications for transplantation in chronic liver disease

- Cirrhosis with complications:
  - Synthetic dysfunction: MELD >15 (Box 4.47), UKELD >49 (Box 4.48).
  - Diuretic-refractory ascites.
  - Recurrent ▲ **hepatic encephalopathy** ▲.
  - ➔ Spontaneous bacterial peritonitis.
- ➔ Hepatocellular carcinoma.
- Polycystic liver disease.
- Inherited metabolic disorders.
- Intractable itch in ➔ primary biliary cholangitis.
- Recurrent life-threatening biliary sepsis in ➔ primary sclerosing cholangitis.
- ➔ Hepatopulmonary syndrome.
- Failed previous liver transplantation (i.e. primary non-function, hepatic artery thrombosis, disease recurrence).

Box 4.46 Contraindications to liver transplantation

Absolute

- Active alcohol or substance misuse.
- Extrahepatic malignancy.
- Multiorgan failure.
- Advanced cardiorespiratory disease.
- Uncontrolled systemic sepsis.
- AIDS. ❗ HIV itself is not a contraindication, but infected individuals require CD4 count >100/mm^3 and undetectable viral load.
- Severe psychiatric disease refractory to treatment.

Relative

- Age >70y.
- ➔ Portal vein thrombosis with mesenteric vein involvement.
- Cumulative comorbidity.

Table 4.24 Selection criteria for liver transplantation in acute liver failure (King's College criteria)

Paracetamol overdose	Non-paracetamol related
Arterial pH <7.3 following volume resuscitation (irrespective of grade of ▲ **hepatic encephalopathy** ▲)	PT >100s, INR >6.5

Or all three of:
- Pt >100s, INR >6.5
- Creatinine >300μmol/L
- Grade III/IV encephalopathy
	Or any three of:
	- Aetiology:
	  - ➲ Drug-induced liver injury.
	  - Non-HAV/HBV/HCV hepatitis
	- Age <10y or >40y
	- PT >50, INR >3.5
	- Serum bilirubin >300μmol/L
	- Jaundice >7d before encephalopathy

- Arterial lactate >3.5mmol/L at 4h or >3mmol/L at 12h (following volume resuscitation)	

Box 4.47 MELD score

Model for End-stage Liver Disease (MELD) score based on retrospective study of chronic liver disease prognosis in absence of OLT:

$$3.8 * \log_e (\text{biliriubin (mg/dL)}) + 11.2 * \log_e (\text{INR}) + 9.6 * \log_e (\text{creatinine (mg/dL)})$$

- MELD scores range from 6 to 40 (<9 = 4% 3mo mortality, >30 = 83% 3mo mortality).
- Advantage of MELD over ➲ Child–Pugh score is that has no subjective components (e.g. 'clinical' ascites).

In 2002, MELD adopted in USA as means of determining OLT candidate priority for organ allocation.

Box 4.48 UKELD score

UK Model for End-stage Liver Disease (UKELD) score developed from MELD score, incorporating serum sodium:

$$(5.395 * 1n[\text{INR}]) + (1.485 * 1n[\text{creatinine}]) + (3.13 * 1n[\text{bilirubin}]) - (81.565 * 1n[\text{sodium}]) + 435$$

- UKELD score of 49 indicates 9% 1y risk of mortality, and is the minimum score required to be listed for liver transplant in UK.
- Advantage of UKELD is that incorporates serum sodium, and thus better reflects patients with ascites.

Controversy. Liver transplantation for alcoholic hepatitis

Severe acute alcoholic hepatitis was previously considered an absolute contraindication to liver transplantation. However a prospective study of carefully selected cases reported better survival when compared to matched non-transplant patients, and similar survival to other cases with inactive abstinent alcoholic liver disease.[8] In the UK, service evaluation of the role of liver transplantation in these patients was being undertaken, the selection criteria for which presently include:

- 1st presentation with alcoholic liver disease.
- Age ≤40y with no other comorbidities.
- Liver biopsy with confirmation of diagnosis.
- Lille score ≥0.45, with no response to steroids over 7d.
- No previous participation with formal alcohol management programmes, and agreement to engage with addiction/psychiatric services.
- Absence of infection.

Technique

Pre-transplant assessment and surgical approach are outside the remit of this text. For issues related to postoperative care, see ► Approach to the post-liver transplant patient.

Types of transplant

- Organs can be used from donors after brain death (DBD) or after cardiac death (DCD).
- Whole cadaveric graft. Majority of transplants. Totally reliant on limited supply of organs, although recent change in UK law to opt-out (rather than opt-in) programme expected to increase availability.
- Split-liver graft. Also cadaveric, but splitting liver may allow 2 recipients to be transplanted.
- Auxiliary liver transplantation. Donor liver implanted next to part, or whole, of recipient liver. May be used for ▲ **acute liver failure** ▲ when regeneration of native liver might occur, or metabolic liver disease.
- Live-related transplantation. Hemi-hepatectomy and liver lobe donation from a family member.

Post-transplant complications

See ► Approach to the post-liver transplant patient.

Los Angeles grading

See: ➔ Oesophagitis.

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[8] Mathurin P *et al*. (2011). *N Engl J Med* **365**: 1790–800.

Lymphangiectasia

Obstruction of lymphatic drainage from the small intestine, resulting in dilatation of small lymphatic channels in serosa and mesentery. Consequences are ↓ absorption of chylomicrons and fat-soluble vitamins, and excess loss of lymph into lumen causing hypogammaglobulinaemia and lymphopaenia (especially T cells) resulting in loss of cell-mediated immunity. Blockage of lymphatics can result in chylous ascites or pleural effusion. GI symptoms not prominent, although can get diarrhoea, pain, and vomiting. Causes outlined in Box 4.49. Lymphangiectasia may be associated with Noonan, Turner, and Klippel–Trenaunay syndromes.

Diagnosis

Suspect in any patient with unexplained hypoalbuminaemia, especially if lymphopaenia and/or steatorrhoea. Decreased levels of immunoglobulins, transferrin, and caeruloplasmin seen. Associated loss of fat-soluble vitamins can lead to ↓ clotting factors but rarely of clinical consequence. Small bowel biopsy can demonstrate dilated lacteals. Radiology may reveal oedematous bowel folds. Faecal concentrations of α_1-antitrypsin can be used to measure intestinal protein loss (not gastric protein loss, as α_1-antitrypsin degraded at pH <3). Optimal test is to measure clearance during 72h stool collection, with plasma clearance expressed as ml/d. See also: ➲ protein-losing enteropathy.

Treatment

Acquired lymphangiectasia should be treated by correction of primary disease. Congenital lymphangiectasia partially controlled with dietary restriction of long-chain fatty acids with enrichment by medium-chain triglycerides (which do not require lymphatic transport).

Lymphomas in GI tract

Solid malignancies of lymphoid tissue. GI tract very rarely affected by Hodgkin's lymphoma, but accounts for 30–40% of extranodal non-Hodgkin's lymphoma.

Box 4.49 Causes of lymphangiectasia

Primary (congenital)

Asymmetric lymphoedema dating from infancy or early childhood.

Secondary (acquired)

- Abdominal or retroperitoneal carcinoma.
- ➲ Chronic pancreatitis.
- Mesenteric TB.
- ➲ Sarcoidosis.
- ➲ Crohn's disease.
- ➲ Whipple's disease.
- ➲ Systemic sclerosis.
- Cardiac: constrictive pericarditis, congestive heart failure.
- ➲ Systemic lupus erythematosus.

Oesophageal lymphoma

Rare: 1% of all GI lymphomas. Involvement usually due to spread from proximal stomach. Variable presentation, with poor prognosis. Should be considered in patients with significant immunosuppression.

Gastric lymphomas

- Accounts for 5% of gastric neoplasms (see also ➔ gastric cancer and ➔ gastrointestinal stromal tumours). Great majority are B cell lymphomas, either non-Hodgkin's or low-grade mucosa-associated lymphoid tissue (MALT) lymphomas (MALTomas). Latter account for 40% of primary gastric lymphomas.
- The term 'MALT lymphoma' has come to be used interchangeably with marginal zone B cell lymphoma, which in stomach is associated with ➔ *Helicobacter pylori* infection. *H. pylori* found in up to 98% of cases of MALT lymphoma, with cagA-positivity particularly linked. Incidence ~1/50,000 *H. pylori*-infected people. MALT lymphomas usually found in antrum, but may be multifocal. Tend to metastasize late.
- About 50% of gastric lymphomas are diffuse large B cell lymphomas. Relationship to *H. pylori* uncertain, but these tumours are high grade and do not respond to antibiotics alone. Treatment chemoradiotherapy, as surgery no longer needed for diagnosis or staging.
- Early gastric lymphomas may be asymptomatic, but later clinical presentation similar to gastric cancer; night sweats and fever may be prominent. Polypoid, fungating mass may be seen, and be difficult to distinguish endoscopically from adenocarcinoma. Endoscopy and biopsy 95% sensitive, and EUS allows assessment of disease stage. CT used to assess distant spread.
- Eradication of *H. pylori* may lead to complete remission of MALT lymphoma in >80% of cases, but for *H. pylori*-negative cases, or where eradication has not induced remission, newer agents including monoclonal antibodies against B cell antigen CD20 (e.g. rituximab) show promise.

Small bowel lymphomas

- B cell lymphomas encompass immunoproliferative small intestinal disease (IPSID) and non-IPSID subtypes, including marginal zone B-cell lymphoma (MALT type, but not associated with *H. pylori*), large B cell lymphoma, mantle cell lymphoma, follicular lymphoma, and Burkitt's lymphoma. T cell lymphomas usually associated with ➔ coeliac disease.
- Of the B cell small bowel lymphomas, marginal zone and follicular lymphomas regarded as indolent processes: incurable but controllable by chemotherapy. Diffuse large cell lymphomas and mantle cell lymphomas more aggressive and require chemotherapy.

- Enteropathy-associated T cell lymphoma occurs as complication of ➔ coeliac disease. Intraepithelial T cells in coeliac disease $CD3^+CD8^+$ and polyclonal. Monoclonal proliferation of T cells can result in a spectrum of processes from refractory sprue (where response to gluten-free diet is lost), through ulcerative jejunitis to enteropathy-associated intestinal T cell lymphoma. Clinical features include diarrhoea, abdominal pain, weight loss, and vomiting. Minority present with intestinal perforation or obstruction. Anaemia common, albumin usually low, and LDH ↑ in 25%. Treatment usually combined surgery and chemotherapy, but prognosis poor (response rate 60%, remission rate 40%, and relapse in 6mo in 80%). Survival 30–40% at 1y, and 10–20% at 5y.

Immunodeficiency-related lymphoma

- PTLDs occur in 1–20% of solid organ transplants (e.g. ➔ liver transplantation) and bone marrow transplants. Usually result from proliferation of Epstein–Barr virus transformed cells. Treatments include antiviral agents, B cell antibodies (rituximab), and donor leucocyte infusions.
- B cell non-Hodgkin's lymphoma can develop in HIV-infected patients. EBV implicated in ~50%.

Section 4

M

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Mallory–Weiss tears

First described by Quincke in 1879; Mallory and Weiss described 15 cases in 1929. Lacerations in region of gastro-oesophageal junction, often caused by retching. Account for 5–10% of ▲ **upper GI bleeding** ▲. Stops spontaneously in 80–90% and re-bleeding rare. Diagnosis is usually clinical, management conservative, and does not typically require endoscopy. However, endoscopic therapy may be necessary if haemorrhage uncontrolled. Surgical intervention very rare.

Magnification endoscopy

Conventional endoscopy resolution 100,000–200,000 pixels. Magnification endoscopes allow adjustable focusing, enlarging images 1.5–150-fold. Often combined with stains. Current trial data mainly in field of ➲ Barrett's oesophagus. Whether will ↓ need for biopsy or ↑ diagnostic yield over conventional techniques remains to be determined.

MALT lymphoma

See: ➲ Lymphomas in GI tract.

Manometry

- Measuring GI intraluminal pressure is one way of studying motility, abnormalities of which cause several common clinical problems. See entries under ⊳ Clinical Practice and Diagnostics (p. 154, 156 and 157), ➲ oesophageal motility disorders, and ➲ sphincter of Oddi dysfunction.
- Bravo monitoring, using endoscopically placed catheter-free system, allows prolonged oesophageal monitoring. Particularly suitable for patients who cannot tolerate naso-oesophageal catheter. Radiotelemetric capsule attached to oesophageal mucosa 6cm above z-line transmits pH data to portable receiver over 48h.
- Gastroduodenal manometry is established as a research tool but not widely used, partly because mild-to-moderate symptoms correlate poorly with manometric findings and partly because techniques are rather invasive and prolonged (usually require longer procedure than oesophageal manometry and sedation, so reserved for complex motility disorders in regional centres).

Mayo score

A disease activity index, developed to assess severity of ➔ ulcerative colitis. Principally used in clinical trials, but can help evaluate and monitor patients with known disease. Scores from 0 to 12, derived as sum of 4 components (see Table 4.25 and Box 4.50). If endoscopy results are not available, can calculate 'partial' score with other components, ranging from 0 to 9. An online calculator 🖱 http://www.mdcalc.com/mayo-score-disease-activity-index-dai-ulcerative-colitis/ is available. In recent years, there has been a move towards removal of the Physician's Global Assessment due to its subjectivity, resulting in a 'modified' Mayo score ranging from 0 to 9.

Interpretation

Not rigidly defined, but most frequently:

- Moderate or severe disease: score ≥6, with endoscopic subscore ≥2.
- Response to therapy: ↓ of ≥3 points from baseline.
- Remission: score ≤2, with all individual categories ≤1.
- Mucosal healing: endoscopic subscore of 0 or 1, with caveat that in this circumstance friability must be absent.

❗Box 4.50 Pitfalls with interpretation of Mayo score

- Not designed to:
  - Diagnose ulcerative colitis.
  - Predict need for admission or surgical therapy.
- For stool frequency, patient acts as own point of reference. No universal agreement as to whether baseline should be normal for patient before or after the diagnosis of colitis.
- Some argue ongoing rectal bleeding incompatible with remission.
- Physician's Global Assessment criticized for degree of subjectivity. Indications regulatory agencies want this component removed, although captures aspects of disease not otherwise incorporated.

Meckel's diverticulum

Anatomy

Arise from persistence of omphalomesenteric or vitelline duct, which connects embryonic gut tube with yolk sac but normally disappears early in foetal life. Most common congenital GI tract abnormality (Fig. 4.14 and Box 4.51). Can be as proximal as ligament of Treitz, but most within 100cm of the ileocaecal valve. Associated with other congenital anomalies (cleft palate, annular pancreas). Can contain heterotopic rests of gastric (60%) or pancreatic tissue (6%).

Clinical features

Majority asymptomatic, but can present with painless ▲ **lower GI bleeding** ▲. Diverticulitis, perforation, and carcinoma much less frequent. Functional symptoms can arise from heterotopic tissue.

Box 4.51 'Rule of 2' for Meckel's diverticulum

- Present in **2%** of population.
- Usually located **2 feet** proximal to ileocaecal valve.
- Typically **2 inches** in length.

Table 4.25 Mayo score for ulcerative colitis

Item	Description	Score
Stool frequency	Normal	0
	1–2 stools/d more than normal	1
	3–4 stools/d more than normal	2
	>4 stools/d more than normal	3
Rectal bleeding	None	0
	Visible blood in stool less than half the time	1
	Visible blood in stool half the time or more	2
	Passing only blood	3
Mucosal appearance at endoscopy	Normal or inactive disease	0
	Mild disease (erythema, ↓ vascular pattern, mild friability)	1
	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
	Severe disease (spontaneous bleeding, ulceration)	3
Physician rating of disease activity*	Normal	0
	Mild	1
	Moderate	2
	Severe	3

*Accounts for other features including abdominal pain, extraintestinal manifestations, fever, tachycardia, functional status, and patient overall sense of well-being.

Diagnosis

Technetium pertechnetate ('Meckel's) scan detects uptake by heterotopic gastric mucosa. False-positives may occur with ➔ intussusception and ➔ Crohn's disease.

Management

Surgical resection for symptomatic diverticula.

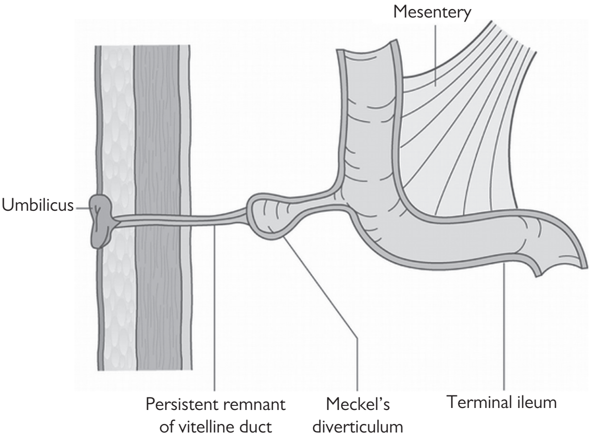

Fig. 4.14 Meckel's diverticulum.

Megacolon

Defined as a radiological diameter of rectosigmoid or descending colon >6 cm, ascending colon >8cm, or caecum >12cm. Can be **congenital** (➲ Hirschsprung's disease, and other abnormalities resulting in autonomic denervation) or **acquired** (can be associated with any cause of ➲ constipation, and rarely ➲ trypanosomiasis in Chagas' disease). See also ➲ toxic megacolon.

- Acquired megacolon assumed if no congenital lesion or symptoms did not appear in infancy. Look for underlying cause (Box 4.52).
- Idiopathic megarectum and megacolon relate to dilatation in absence of demonstrable organic disease. Patients with megarectum are young and tend to present with faecal soiling and impaction.

Diagnosis

Plain AXR may identify megacolon but further investigations required to establish aetiology. CT (normally with water-soluble contrast) useful for defining colonic anatomy and any mechanical obstruction. Anorectal manometry helpful for differentiating congenital from acquired causes. Colonic transit usually delayed in those with idiopathic megacolon but may be normal in those with isolated megarectum.

Box 4.52 Causes of acquired megacolon

- Neurological:
  - Chagas’ disease.
  - ➔ Parkinson’s disease.
  - Myotonic dystrophy.
  - Autonomic neuropathy, including in ➔ diabetes.
- Smooth muscle:
  - ➔ Systemic sclerosis.
  - ➔ Amyloidosis.
- Metabolic:
  - Hypothyroidism.
  - Hypokalaemia.
  - ➔ Porphyria.
  - Phaeochromocytoma.
- Drugs:
  - Opioids.
  - Anticholinergics.
  - Antipsychotics.
- Mechanical obstruction.

Management

- In general, management of chronic megacolon is similar to that of chronic constipation. Optimal treatment is to empty bowel completely (phosphate enemas) then titrate an osmotic laxative. Disimpaction may be required.
- Stimulant laxatives should be avoided.
- Prucalopride (prokinetic) 1–2mg PO od may be considered.
- Trial of pyridostigmine (acetylcholinesterase inhibitor) taken 30min before food is another alternative.
- Lifelong laxatives usually needed and follow-up important.
- Behavioural therapy can be helpful.
- Occasionally, colectomy may be considered for patients with intractable and life-limiting symptoms.
- Acute or ➔ toxic megacolon covered separately.

Melanosis coli

Brown discoloration of colonic epithelium caused by accumulation of lipofuscin pigment in lamina propria macrophages resulting from laxative-induced apoptosis. Found in 70% of people who use anthraquinone laxatives (cascara, aloe, senna, rhubarb). Disappears within 12mo of stopping laxatives. Colonic tumours lack pigment-containing macrophages and thus very easily seen (Plate 35).

MELD score

See: ➔ Liver transplantation.

Ménétrier's disease

- Characterized by giant hypertrophic gastric folds, mainly involving fundus. Enlarged folds also seen in other conditions, e.g. ➲ gastrinoma. Associated hypochlorhydria, hypergastrinaemia, excess mucus production, and hypoalbuminaemia (due to protein-losing gastropathy). Cause uncertain, but ↑ expression of epidermal growth factor (EGF). High prevalence of ➲ *H. pylori*.
- Symptoms include epigastric pain (may mimic ➲ peptic ulcer), nausea, peripheral oedema, anorexia, and weight loss. Premalignant condition, with ➲ gastric cancer in 10–15%.
- Diagnosis often made on endoscopy, but full-thickness biopsy required for complete assessment. Histological changes of marked foveolar hyperplasia, glandular atrophy, and ↑ mucosal thickness.
- Little controlled data on treatment, but may respond to *H. pylori* eradication, CMV eradication with → GANCICLOVIR in paediatric disease, acid suppression (→ PROTON PUMP INHIBITORS, → H_2 RECEPTOR ANTAGONISTS), → CORTICOSTEROIDS, or → octreotide. Clinical efficacy of monoclonal antibodies against EGF receptor (e.g. cetuximab) reported. Partial/total gastrectomy reserved for refractory/recurrent bleeding, severe hypoproteinaemia, or gastric cancer.

Mesenteric venous thrombosis

Accounts for 2–10% of cases of acute mesenteric ischaemia. Infarction unusual unless branches of peripheral arcades and vasa recta involved. Causes similar to those for ➲ portal vein thrombosis.

Clinical features

Acute mesenteric venous thrombosis presents with pain in 90%. Lower GI bleeding or haematemesis occur in 15% and suggest infarction. Most patients febrile, and 25% septic. Patients with **chronic mesenteric venous thrombosis** usually asymptomatic at time of diagnosis but may bleed from varices secondary to ➲ portal vein thrombosis.

Risk factors

Broadly divided into inherited or acquired:

- **Inherited thrombophilias** (e.g. factor V Leiden deficiency, protein C or S deficiency).
- **Acquired:**
  - Intra-abdominal inflammation (IBD, pancreatitis, diverticulitis).
  - Abdominal mass.
  - Portal hypertension.
  - Acquired thrombophilia (e.g. antiphospholipid syndrome).
  - Myeloproliferative disorders (e.g. polycythaemia rubra vera).
  - Endoscopic sclerotherapy.

Diagnosis

Selective angiography can establish definitive diagnosis and differentiate arterial from venous ischaemia, but not always available in emergency. CT angiography probably investigation of choice (but ensure adequate portal venous phase). If no obvious predisposing illness found, patients should be tested for hypercoagulable conditions.

Treatment

Most patients with acute mesenteric venous thrombosis treated as for ➲ intestinal ischaemia. Surgery indicated if any signs of bowel infarction; if required, postoperative heparinization ↓ recurrence and progression. Treatment of chronic mesenteric venous thrombosis centres on controlling bleeding from varices.

Microscopic colitis

Two distinct diseases, **collagenous colitis** and **lymphocytic colitis**, united by their clinical presentation of watery diarrhoea with endoscopically normal colonic mucosa but histological inflammation.

Epidemiology

Mean age at diagnosis 65y, although 25% of patients younger than 45y. Recognized in both sexes, with ♀ preponderance (particularly collagenous colitis). Incidence: 8.6/100,000 person-years. Historically under-reported because of failure to biopsy mucosa of normal appearance in patients with watery diarrhoea. Association with ➲ coeliac and autoimmune disease, and some medications (e.g. NSAIDs).

Pathology

In collagenous colitis, there is a thickened subepithelial collagen layer, >10μm thick. Tends to be collagen types I and III rather than normal type IV, and more common on right side of colon. Collagen band may partly result from ↓ collagenases rather than ↑ deposition, and thickness does not correlate with clinical severity. May be secondary phenomenon rather than causative of diarrhoea.

In lymphocytic colitis, there are >20 intraepithelial lymphocytes per high power field.

Aetiology and pathogenesis

Thought broadly to involve epithelial immune responses to antigens derived from luminal contents. Faecal diversion produces improvement but condition relapses once intestinal continuity re-established. Dietary factors, intestinal pathogens, smoking, drugs (particularly NSAIDs) and toxins have all been proposed as causative factors. Bile acid malabsorption also postulated to play role in pathogenesis.

Clinical features

Usually chronic watery diarrhoea, sometimes with cramping abdominal pain and weight loss. Examination normal.

Diagnosis

- Routine blood tests normal. ➲ Coeliac screen in collagenous colitis.
- Stool microscopy: positive for leucocytes in 50%, but no RBCs.
- ⊳ Faecal calprotectin ↑ in approximately 2/3 of patients, but not as sensitive as for ➲ Crohn's disease or ➲ ulcerative colitis.
- Colonoscopy with biopsies required for diagnosis.

Treatment

- → BUDESONIDE 9mg/d PO for 6wk to induce remission. Two trials show maintained response rate of 80% with 6mg/d for 6mo, although long-term treatment with steroids undesirable.
- Some evidence to support → MESALAZINE (up to 4.8g/d), possibly with addition of bile salt-binding agent such as → COLESTYRAMINE or → COLESEVALAM.
- Loperamide may be helpful in relieving symptoms.
- No benefit shown for probiotic therapy.
- Severe cases may need immunomodulators such as → AZATHIOPRINE or → METHOTREXATE, or → anti-TNF agents.
- Surgery required in very rare cases.

Prognosis

Course chronic with frequent relapses in ≈50%.

Microsporidia

Obligate intracellular protozoa that cause disease principally in immunocompromised. Mainly seen in HIV-infected patients with CD4 count <100/mm^3, but also transplant recipients. Most common are *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*, which infect the small intestine and cause severe diarrhoea, bloating, nausea, and loss of appetite. Can disseminate in severe immunocompromise resulting rarely in granulomatous hepatitis, cholangitis/cholecystitis, tubulointerstitial nephritis, or keratoconjunctivitis. Diagnosed on stool microscopy or mucosal biopsy (Giemsa or modified trichrome stain, or electron microscopy), or PCR (most sensitive). Treatment largely supportive, alongside optimization of HAART in HIV-infected patients and reduction in immunosuppression in transplant recipients. If no response, albendazole 400mg PO bd for 21d may be required.

Mirizzi's syndrome

Impaction of gallstone in cystic duct, with obstruction of adjacent common bile duct/common hepatic duct. Presents with jaundice, RUQ pain and fever, and may mimic ➲ choledocholithiasis or ➲ cholangitis. Distended gallbladder can be palpable and tender (see ➲ cholecystitis), and gallbladder empyema may develop. US reveals biliary dilatation above the cystic duct. ERCP may demonstrate obstructing stone and ➲ biliary stricture in region of common hepatic duct with obstructed cystic duct (features may mimic ➲ cholangiocarcinoma).

Endoscopic stone removal (via ▷ ERCP) often challenging. Definitive treatment usually surgical, with cholecystectomy and surgical repair of bile duct if necessary (Fig. 4.15).

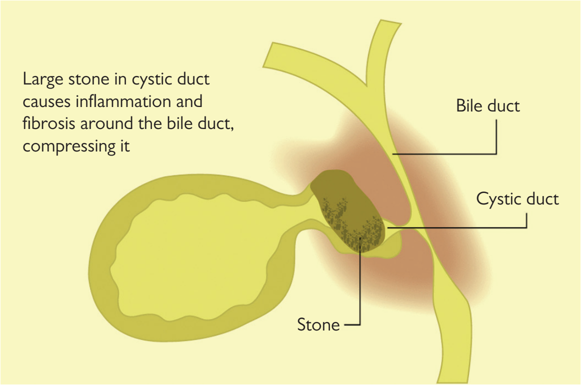
Large stone in cystic duct causes inflammation and fibrosis around the bile duct, compressing it
Bile duct
Cystic duct
Stone

Fig. 4.15. Mirizzi syndrome, where a cystic duct stone obstructs the common hepatic or biliary duct. Reproduced with permission from Firth, John, *et al*. *Oxford Textbook of Medicine* 6e, 2020, Oxford University Press.

Multiple endocrine neoplasia (MEN)

MEN should be considered in all patients with ➲ pancreatic endocrine tumours. Three main syndromes:

- **MEN-1** (Werner syndrome). Autosomal dominant. Hyperparathyroidism in >90%, pancreatic neuroendocrine tumours (NET) in 80% (mainly ➲ gastrinoma and insulinoma), and pituitary adenomas (usually prolactin secreting). Gene defect on chromosome 11 in *menin*. Pancreas demonstrates diffuse microadenomatosis, but in those with Zollinger–Ellison syndrome 80% of gastrinomas are in duodenum, not pancreas.
- **MEN-2a** (Sipple syndrome). Phaeochromocytoma (20–40%) and bilateral medullary thyroid carcinoma. Mutations in *RET*.
- **MEN-2b** Similar to MEN-2a, but thyroid carcinoma at younger age and more aggressive + marfanoid features and mucosal neuromas.

Section 4

N

Nematodes: see ➲ Roundworm (nematode) infection *460*
Neuroendocrine tumours (NETs) *460*
Nodular regenerative hyperplasia (NRH) *461*
Non-alcoholic fatty liver disease (NAFLD) *462*
Non-steroidal anti-inflammatory drugs (NSAIDs) and the GI tract *464*
Non-ulcer dyspepsia: see ► Approach to dyspepsia and gastro-oesophageal reflux *466*
Norwalk virus: see ► Approach to acute diarrhoea *466*

Nematodes

See: ➔ Roundworm (nematode) infection.

Neuroendocrine tumours (NETs)

Background

NETs within the GI tract may be classified into non-functioning (no hormone-related clinical features) and functioning (cause symptoms due to peptide and hormone release) tumours.[1] Particular systemic syndromes are caused by hormones and biogenic amines released from cytoplasmic membrane-bound neurosecretory granules. Approximately 80% of patients with multiple endocrine neoplasia type 1 (MEN-1) have pancreatic tumours. General incidence of gastrointestinal NETs is 2-3/100,000 persons/y, but thought to be rising. Most commonly identified in small intestine or pancreas.

Investigation

Aim is to identify primary tumour, possible metastases, and presence of functional activity.

Imaging

- **Endoscopy.** Initial investigation for suspected gastric, duodenal, and colorectal lesions. EUS is an adjunct to assess depth of invasion, guide biopsy, and detect small pancreatic lesions. Capsule endoscopy can identify small bowel NETs if other modalities have failed.
- **CT and MRI.** Useful for small bowel and pancreatic NETs.
- **Scintigraphy.** Pancreatic NETs often express high levels of somatostatin receptors and can be imaged with the radiolabelled somatostatin analogue octreotide. Accuracy has improved with addition of SPECT. Gallium-68 octreotate PET now increasingly used. Several novel tracers becoming available at specialist centres which hold promise for improved detection and staging.

Biochemistry

- 24h urine collection for 5-HIAA and catecholamines.
- ➢ Gut hormone profile. Usually includes gastrin, VIP, glucagon, somatostatin, and chromogranin A (p. 148).

Histology

- Shows small cells with regular round nuclei. Stain positive for neuroendocrine markers, including neuron-specific enolase, synaptophysin, and chromogranin. Tumours graded on the basis of morphological criteria and proliferative activity.

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[1] Halperin DM *et al* (2015). *Annu Rev Med* **66**: 1–16.

Clinical features

May be asymptomatic (e.g. incidental lesion seen on abdominal US), present with syndromes related to hormone release (functioning tumours, Table 4.26), or mass effect of primary/metastatic disease.

Table 4.26 Functional NET syndromes

Functioning tumour	Symptoms
Insulinoma	Confusion, sweating, dizziness, weakness, unconsciousness, relief with eating, weight gain (all related to hypoglycaemia)
Gastrinoma	Zollinger-Ellison syndrome: severe peptic ulceration and diarrhoea, or diarrhoea alone
Glucagonoma	Necrolytic migratory erythema, weight loss, diabetes mellitus, stomatitis, diarrhoea
VIPoma	Verner-Morrison syndrome: profuse watery diarrhoea with marked hypokalaemia
Somatostatinoma	Cholelithiasis, weight loss, diarrhoea and steatorrhoea, diabetes mellitus

Management

Surgical cure should be the goal, although palliative approach often necessary. NETs commonly slow growing.

- Referral to specialist unit for multidisciplinary approach crucial.
- Surgery is the only curative option and attempted for localized disease (see ➜ carcinoid and ➜ pancreatic endocrine tumours).
- Palliative approaches to metastatic NETs include systemic chemotherapy, somatostatin analogues (e.g. octreotide, lanreotide), and ^{131}I-MIBG if diagnostic scintigraphy positive.
- Options for liver lesions (most common site for metastases) include surgical resection, embolization, radiofrequency ablation, and (rarely) ➜ liver transplantation.

Nodular regenerative hyperplasia (NRH)

Nodular regenerative hyperplasia is a cause of non-cirrhotic portal hypertension. Patients may present with features of portal hypertension (i.e. ascites or variceal bleeding), but liver function usually preserved. Aetiology unknown but common associations shown in Box 4.53.

Diagnosis

May be difficult. Histology shows nodule formation, phlebosclerosis, and dense portal fibrosis but without fibrous septae (in contrast with cirrhosis). Nodules usually 0.2–2cm and may be seen on imaging (hypodense on CT), as may splenomegaly. Finding of pre-sinusoidal portal hypertension on vascular studies in presence of patent portal vein supports diagnosis.

Treatment

Based on management of ➔ portal hypertension.

Box 4.53 Causes of NRH

- Prothrombotic disorders (e.g. protein C and S deficiency).
- HIV.
- Rheumatoid arthritis.
- SLE.
- Polyarteritis nodosa.
- Drugs: azathioprine, didanosine, cyclophosphamide.

Non-alcoholic fatty liver disease (NAFLD)

Background and aetiology

- NAFLD describes a chronic liver disease with histological features similar to ➔ alcoholic liver disease, but without significant alcohol intake. Now the most common liver disorder in the developed world.
- Can be divided into NAFL (non-alcoholic fatty liver), NASH (non-alcoholic steatohepatitis), and NASH cirrhosis.
- Increasing prevalence closely parallels rate of obesity in population; 25–34% of patients have fatty liver (and 3% NASH) in US studies.[2] Reports suggest 9.6% of US children age 2–19 have NAFLD.
- NAFLD is hepatic manifestation of the metabolic syndrome (insulin resistance, diabetes, hyperlipidaemia, obesity, and hypertension).
- Hepatic steatosis can cause direct hepatocellular injury, which can lead to progressive fibrosis and cirrhosis. A 'second hit' liver injury also occurs, triggered by oxidative stress, mitochondrial abnormalities, and hormonal changes that activate hepatic stellate cells.

Clinical features

- Most patients asymptomatic, with diagnostic suspicion raised by incidental ↑ LFTs (usually ALT or γGT) or 'fatty liver' on US. Jaundice rare. Fatigue, malaise, and RUQ discomfort may be reported.
- Hepatomegaly common.
- Can progress to end-stage liver disease and portal hypertension. Natural history study over 14y from Sweden showed that 47% with steatosis alone progressed to fibrosis, and 36% with NASH at outset progressed to cirrhosis/severe fibrosis.
- As with other aetiologies of chronic liver disease, ↑ risk of ➔ hepatocellular carcinoma. Cardiovascular and liver-related deaths also raised.
- Differential diagnosis listed in Box 4.54.

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[2] Rinella ME (2015). *JAMA* **313**: 2263–73.

Box 4.54 Differential diagnosis of NAFLD

- Significant alcohol use.
- Starvation.
- Pregnancy-related hepatic steatosis.
- ➲ Parenteral nutrition.
- Jejunal-ileal bypass.
- ➲ Hepatitis C (especially genotype 3).
- Drugs (amiodarone, methotrexate, tetracycline).
- Metabolic disorders (➲ abetalipoproteinaemia, glycogen storage disease, ➲ Wilson's disease).

Investigation

- Important to exclude other causes of chronic liver disease (see ► Approach to well patients with abnormal liver tests), including careful alcohol history. NIH definition requires alcohol intake <18U/wk for ♂, <9U/wk for ♀ for NAFLD to be diagnosed.
- Characteristic pattern of LFTs shows ↑ ALT/AST and ↑ GGT (ALP usually normal) with ↑ fasting cholesterol and glucose. Elevated serum ferritin may be seen. Role of *HFE* ➲ haemochromatosis gene heterozygosity in accelerated fibrosis controversial.
- US, CT, and MRI all accurate at showing fatty liver.
- Liver biopsy is the only definitive way to define injury (LFT derangement poorly predicts fibrosis, and ~20% of patients with persistent ↑ ALT have advanced fibrosis/cirrhosis). No clear guidelines that identify which patients require biopsy (see 💣 Controversy). Histology may show steatosis (fatty liver), steatohepatitis (with inflammation), or established fibrosis. However, now increasing use of Fibroscan to identify advanced fibrosis.

💣 Controversy. Liver biopsy in NAFLD

Role of liver biopsy remains controversial, as carries definite risk. Many hepatologists advise initial identification and treatment of risk factors prior to biopsy in otherwise uncomplicated cases. Several non-invasive methods now used to detect fibrosis. We recommend use of ➲ Fib-4 index (combines platelet count, ALT, AST, and age), which will help identify patients with moderate/severe fibrosis who may require biopsy. ➲ Fibroscan (using XL probe) also useful.

Management

- Cornerstone is risk factor control (weight loss, treat hyperlipidaemia and hyperglycaemia, and discontinue possible contributing drugs). However, these measures are only effective in minority.
- 7% weight reduction leads to histological improvement.
- Bariatric surgery (including Roux-en-Y gastric bypass) may lead to significant improvement, with histological improvement in 89–94%.
- Statins generally safe but do not improve histology.
- No drug therapy yet shown to be beneficial. Early promise with metformin proven unfounded. Pioglitazone improves histological appearances, although long-term safety and efficacy not yet established.[3]

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[3] Sanyal AJ *et al.* (2010). *N Engl J Med* **362**: 1675–85.

Guideline

American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association practice guideline on diagnosis and management of non-alcoholic fatty liver disease (2012).

Non-steroidal anti-inflammatory drugs (NSAIDs) and the GI tract

Background

- NSAIDs, even low-dose aspirin, cause bleeding and ulceration in the GI tract. Erosions seen in 30–50% of patients (associated with iron deficiency, but rarely severe adverse events), ulcers in 10-30%, and serious complications in 1–2%.
- Most attention has focused on upper GI tract (relative risk: 4 for gastric ulcers, 2 for duodenal ulcers), although also predispose to:
  - Small bowel ulceration (principally distal jejunum and ileum).
  - Web-like strictures.
  - ➔ Collagenous colitis.
  - Flares of ➔ Crohn's disease and ➔ ulcerative colitis.[4]
  - Bleeding from diverticula or vascular malformations.
- Symptoms are not predictive of mucosal injury, and >50% of patients with serious ulcer complications have no prior warning.
- Conversely, there is evidence NSAIDs (particularly aspirin) may be chemoprotective for ➔ Barrett's oesophagus, ➔ oesophageal cancer, and ➔ colorectal cancer. Trials ongoing to verify efficacy and determine optimum dosing.[5]

Mechanism of injury

Damage occurs through local and systemic mechanisms. NSAIDs are directly cytotoxic to GI epithelial cells, and topical injury is largely prevented by enteric-coated preparations, although may also attenuate antiplatelet activity of low-dose aspirin. Systemic damage results from cyclo-oxygenase (COX) inhibition (principally COX-1 isoform), which reduces mucosal prostaglandin and bicarbonate synthesis, blood flow (nitric oxide dependent), and systemic platelet function.

Risk factors

Risk factors for NSAID-associated complications are shown in Box 4.55. Role of ➔ *H. pylori* uncertain but current consensus favours it as an independent risk factor. Relative frequency of GI injury with different NSAIDs generally correlates with degree of COX-1 inhibition: ibuprofen lowest risk; indometacin and piroxicam highest.

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[4] Habib I *et al.* (2014). *Inflamm Bowel Dis* **20**: 2493–502.

[5] Sahin IH *et al.* (2014). *Cancer Lett* **345**: 249–57.

Box 4.55 Risk factors for NSAID-induced ➲ peptic ulceration

- Age >65.
- Previous ulcer disease.
- High-dose NSAIDs.
- Chronic major organ impairment (including liver cirrhosis).
- Concomitant antiplatelet or anticoagulant use.
- Concomitant corticosteroids.
- Concomitant SSRI use.
- Alcohol and tobacco use.
- *H. pylori* infection (although eradication not proven protective).

Strategies to limit GI toxicity with NSAIDs

- Limit course duration and dose.
- Enteric-coated preparations. However, while these protect against gastric and duodenal ulceration, trade-off is that they limit antiplatelet efficacy of aspirin, and ↑ risk of enteropathy.
- Topical preparations. Effective in arthritis, with better safety profile.
- Co-administer with gastroprotective agents:
  - → ANTACIDS, → H_2RAS, → PPIS, and → MISOPROSTOL all attenuate NSAID-induced upper GI mucosal injury (to varying degrees).
  - PPIs generally 1st line. More effective than H_2RAs, and equally effective but better tolerated than misoprostol. Not protective against enteropathy.
  - H_2RAs offer some protection, and may avoid some side-effects associated with long-term PPI use.
  - Misoprostol as effective as PPIs for preventing upper GI ulceration, and may also protect against lower GI complications. Dose of 800μg/d more effective than 400μg/d, but usually restricted by side-effects (principally diarrhoea). Most commonly prescribed at low dose in combination tablet with diclofenac. Absolutely contraindicated in pregnancy (causes miscarriage in early pregnancy, and induces labour in 3rd trimester).
- ➲ *H. pylori* eradication. Efficacy not yet proven.
- COX-2 selective NSAIDs (-coxibs):
  - There are two COX isoforms: COX-1 (constitutively expressed; involved in mucosal blood flow, platelet aggregation and regulation of gastric acid) and COX-2 (inducible; major source of pro-inflammatory eicosanoids).
  - Consequently, COX-2 selective inhibitors were developed as anti-inflammatory drugs that should have minimal GI side-effects.
  - Despite initial enthusiasm, major concerns have now been raised about their safety and cost-efficiency (see 💣Controversy).
  - In general, coxibs no more effective for gastroprotection than non-selective NSAIDs combined with PPI, but cost more.[6]
  - Benefit lost if patient co-prescribed low-dose aspirin.
  - Therapy can be tailored to complication encountered: NSAID + PPI more effective for dyspepsia, coxib for enteropathy.
  - Moderate quality evidence supports combining COX-2 selective inhibitors with PPIs for patients at very high risk of GI bleed.

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[6] Wang X *et al*. (2011). *Eur J Gastroenterol Hepatol* **23**: 876–80.

- Novel NSAIDs being developed that may have enhanced safety profiles. These include agents that co-release nitric oxide or hydrogen sulphide (enhance mucosal blood flow), provide dual COX and 5-lipooxygenase inhibition, or selectively inhibit microsomal PGE_1.

Controversy. Utility and risks of coxibs

- Celecoxib was the first COX-2 selective inhibitor, released in 1999. Rofecoxib marketed same year.
- Initial studies reported reduction in GI side-effects.
- However, these were later criticized for use of:
  - Inappropriate end-points. Often combined outcomes that included (and biased towards) endoscopically-detected silent lesions rather than clinically significant bleeds or ulcers.
  - Inappropriate comparators. Usually placebo or non-selective NSAID monotherapy. Conversely, comparisons to 'best established practice' of NSAID + PPI showed equal efficacy.
  - Failure to examine impact on lower GI side-effects.
  - In September 2004, rofecoxib withdrawn following identification of increased cardiovascular toxicity. Subsequently concerns raised about all coxibs, as a drug class.
  - In fact, further meta-analyses suggest cardiovascular toxicity increased equally with all NSAIDs (non-selective and COX-2 inhibitors alike), with possible exception of naproxen.

Drug-induced liver injury (DILI)

Given their widespread use, NSAIDs account for 10% of all ➔ drug-induced liver injury (although individual patient risk is low). Incidence: 3–23/100,000. Several withdrawn from market because of hepatotoxicity. Ibuprofen safest, likely due to short plasma half-life and lack of toxic metabolites. Sulindac and nimesulide high risk. Aspirin hepatotoxicity is dose-dependent, and risk of Reye's syndrome in children (mitochondrial dysfunction leading to free fatty acid hepatic accumulation, massive steatosis, metabolic acidosis, encephalopathy, hypoglycaemia, coagulopathy, and azotaemia).

Non-ulcer dyspepsia

See: ► Approach to dyspepsia and gastro-oesophageal reflux.

Norwalk virus

See: ► Approach to acute diarrhoea.

Section 4

O

Obesity surgery: see ▸ ‘Anti-obesity (bariatric) surgery’ (p. 182), and ► Approach to obesity *468*
Obstetric cholestasis *468*
Occult blood: see ▸ Faecal occult blood testing *469*
Oesophageal motility disorders *469*
Oesophageal rings *471*
Oesophageal stricture *472*
Oesophageal tumours *473*
Oesophagitis *477*
Ogilvie’s syndrome (acute pseudo-obstruction) *478*
Opioid dependence *478*
Optical biopsy *480*
Oral contraceptive pill (OCP) *480*
Oral rehydration solution (ORS) *481*
Osler–Weber–Rendu syndrome: see ➲ Hereditary haemorrhagic telangiectasia *482*
Osteoporosis and metabolic bone disease: see also ▸ ‘Bone densitometry’ (p. 167) *482*
Overlap syndromes *484*
Oxalate stones *484*

Obesity surgery

See also: ► Approach to obesity and ➢ Anti-obesity (bariatric) surgery. Antiobesity ('bariatric') surgery progressively more common in UK, with >6,000 bariatric operations performed and number ↑ each year. Surgical approaches vary: see ➢ Anti-obesity (bariatric) surgery for details; >95% of procedures now performed laparoscopically, and surgical mortality <0.01%. As well as achieving weight loss, surgery has proved effective treatment for complications of obesity: >60% of patients with type 2 diabetes and/or obstructive sleep apnoea were able to stop treatments for these diseases within 2y of follow-up.

Complications of bariatric surgery

Following surgery, 30% develop ➲ gallstones, and 30% metabolic bone disease including ➲ osteoporosis. Complications usually present in one of five ways:[1]

- **Abdominal pain** May indicate anastomotic problems (leaks, strictures, ulcers), disturbed bowel mobilization (strictures, adhesions, internal hernia), gallstones, or portal vein injury. In patients who have had banding, pain is most commonly due to band malfunction or malposition.
- **Suboptimal weight loss** Early or unusual weight gain should prompt search for leaks and fistulae. After banding, causes include band slippage, pouch enlargement, or insufficient dietary restriction.
- **Diarrhoea** Most common cause is ➲ dumping syndrome. Incidence ↓ if pylorus preserved.
- **GI bleeding** Early causes include anastomotic ischaemia. Erosions or ulcers can occur at band sites or anastomoses.
- Wound infection.

Obstetric cholestasis

Background

- Prevalence: 0.5–1% of pregnancies. In ♀ who develop cholestasis on high oestrogen ➲ oral contraceptive pill, 50% get obstetric cholestasis in subsequent pregnancies. Can rarely occur as sequelae of ovarian hyperstimulation syndrome.
- Cause unclear but defect in a biliary transporter across canalicular membrane (MDR3) has been described.

Clinical features

Usual onset >Wk 25, but may be earlier. Itch predominates (palms and soles). Jaundice uncommon but if occurs usually 2–4wk later. RUQ pain unusual.

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[1] Lee CW *et al.* (2007). *Curr Opin Gastroenterol* **23**: 636–43.

Investigation

- Vital to exclude other causes of cholestasis (e.g. ➲ choledocholithiasis). See ▶ Approach to liver problems in pregnancy.
- ↑ Bn (largely conjugated), but usually <100μmol/L, ↑ ALP (usually <1,000U/L), ↑ AST/ALT (sometimes >1,000U/L). Curiously, γGT often normal. ↑ PT may be due to vitamin K-dependent clotting factor deficiency, rather than liver failure.
- Key test is fasting serum bile acid level (>10μmol/L). Foetal complications associated with level >40μmol/L.
- Imaging with US essential to exclude biliary obstruction.
- Liver biopsy not required, but if performed demonstrates perivenular canalicular cholestasis, bile plugging, and minimal inflammation.

Management

- Symptoms most reliably controlled by delivery.
- → URSODEOXYCHOLIC ACID 10–15mg/kg/d usually very effective at controlling itch. → COLESTYRAMINE is an alternative, but may exacerbate vitamin K deficiency, necessitating parenteral vitamin K in later stages of pregnancy.
- Antihistamines, phenobarbital, *S*-adenosylmethionine (SAMe), and steroids have also been tried.
- Pregnancy should not continue beyond term, and condition carries significant risks, with perinatal mortality up to 35%. Recurrence of cholestasis in future pregnancies in 60%.
- Cholestasis of pregnancy may be a risk factor for liver and biliary disease in later life.

Occult blood

See: ➢ Faecal occult blood testing.

Oesophageal motility disorders

Can be isolated primary disorders, or secondary to diseases such as ➲ systemic sclerosis, Chagas' disease (➲ trypanosomiasis), and ➲ diabetes mellitus. Primary disorders classified using Chicago Classification according to relaxation of lower oesophageal sphincter (LOS, measured by integrated relaxation pressure) and abnormalities of oesophageal peristalsis.

Hypermotility disorders

Non-➲ achalasia disorders of hypermotility and characteristic ➢ oesophageal manometry findings are detailed in Table 4.27.

Considerable overlap exists between these terms. Although stationary manometry remains gold standard, full agreement between this and 24h ambulatory manometry seen in only ≈50% of cases.

Pathology

Poorly defined but may involve ↑ oesophageal sensitivity to cholinergic stimulation.

Table 4.27 Non-achalasia disorders of oesophageal hypermotility

Disorder	Characteristic finding on manometry
Diffuse oesophageal spasm	≥20% premature contractions
Nutcracker oesophagus (hypertensive peristalsis)	Mean DCI >5,000mmHg-s-cm
Jackhammer oesophagus (hypercontractile oesophagus)	≥1 swallow with DCI >8,000mmHg-s-cm
Hypertensive LOS	Mean LOS pressure >45mmHg, LOS relaxation >75%
Non-specific oesophageal motor disorder	Other

Clinical presentation

Chest pain in 90%, can be severe, usually retrosternal, and may radiate to back. May be some persisting discomfort after acute episodes, which can help differentiate from angina. Dysphagia in 30–60%, and heartburn in up to 20%.

Diagnosis

Upper GI endoscopy usually normal, but important step to exclude alternative reasons for symptoms, such as malignancy, ➔ oesophagitis, or stricture. Barium studies, especially after swallowing soft solids, used less frequently due to availability of manometry. However, can still be helpful in certain circumstances because can link faulty transit with symptoms, and show up features such as non-propulsive contractions ('corkscrew oesophagus'). Conventional or high-resolution manometry are the main diagnostic tools.

Manometry vs high-resolution manometry (HRM)

- HRM replacing conventional manometry due to ease and reproducibility of procedure and improved interpretation.
- Has ↑ number of sensors spaced 1cm apart (as opposed to 3–5cm), allowing for simultaneous pressure readings on both sides of sphincters and within oesophagus.
- Provides three-dimensional plotting format called 'oesophageal pressure topography'.

Treatment

These disorders are not progressive and not associated with more serious underlying pathology, so goal is symptom reduction.

- If symptoms suggest abnormal transit (e.g. regurgitation or dysphagia), treatment similar to ➔ achalasia may help, especially if manometry shows abnormalities of LOS. Botulinum toxin type A injections into LOS or balloon dilatation have been used effectively.
- Treating reflux can be dramatically beneficial, even in absence of classical history.
- Therapeutic trial of → NITRATES, calcium channel antagonists (e.g. nifedipine 10mg SL), and → ANTICHOLINERGICS can help. All shown experimentally to produce at least short-term improvement in manometry. Remember nitrates and calcium antagonists may worsen any coexistent reflux.

- The tricyclic antidepressant trazodone is the only agent that has been found to improve symptoms in a prospective controlled study (although improvement did not depend on any change in manometry).

Hypomotility disorders

Usually secondary to systemic disease (Box 4.56). Clinical manifestations include:

- Dysphagia, secondary to impaired peristalsis or associated sicca syndrome in ➲ systemic sclerosis or associated connective tissue disorders.
- Oesophageal reflux due to low pressure LOS. Complications such as ➲ oesophagitis, strictures, and ➲ Barrett's oesophagus more common.

Management of symptoms of impaired GI motility is described elsewhere (see ► Approach to mouth and swallowing problems).

Box 4.56 Causes of impaired oesophageal motility

- 80% of ➲ systemic sclerosis patients have altered oesophageal motility (second most commonly affected organ). Vascular obliteration, secondary fibrosis, reflux, oesophagitis, and Barrett's oesophagus all seen.
- Also seen in mixed connective tissue disease, ➲ rheumatoid arthritis, and ➲ systemic lupus erythematosus.
- ➲ Amyloid.
- Alcohol.
- Myxoedema.
- Multiple sclerosis.
- ➲ Parkinson's disease.
- ➲ Diabetes: 60% of patients with peripheral or autonomic neuropathy have disordered motility, but symptoms only in minority.
- ➲ Pseudo-obstruction.

Oesophageal rings

Mucosal rings, located at gastro-oesophageal junction, first described by Schatzki in 1953. Found in ~6–14% of adult population on barium swallow, but causes symptoms in minority. Usually considered congenital structural variant, although chronic reflux may contribute.

Clinical presentation

Intermittent, non-progressive dysphagia to hurriedly eaten solids (classically bread or meat bolus—'steakhouse syndrome').

Diagnosis

Barium swallow or endoscopy. If using barium, oesophagus must be well distended by getting patient to perform Valsalva manoeuvre, and include solid bolus during examination to identify lesion (Plate 11).

Management

In symptomatic patients, endoscopic dilatation performed using bougies or pneumatic balloons, with intention of splitting ring. Repeat treatments may be required.

Oesophageal stricture

Can be a feature of oesophageal malignancies or due to extrinsic compression. Most common benign cause is acid reflux, but also seen after caustic injury, variceal sclerotherapy, or band ligation, following endoscopic mucosal resection or ablation, and mediastinal chemo/radiotherapy. Prevalence of peptic strictures in patients with reflux ➲ oesophagitis is 8–20% but may be ↓ with widespread use of → PROTON PUMP INHIBITORS. Strictures following endoscopic mucosal resection thought to occur in 1% of procedures. Strongest risk factor is larger resection, particularly ≥50% of oesophageal mucosal circumference.

Treatment

- Centres on endoscopic dilatation and healing oesophagitis.
- Dilatation can be done with Celestin or Savary–Gilliard graded dilators over guidewire, or using through-the-scope (TTS) balloon. Results equally effective, although balloon exerts lower radial force than rigid dilators.
    - Savary–Gilliard dilators preferred for malignant strictures (but dilatation largely replaced by stenting for malignant strictures).
    - Dilatation to 15mm generally relieves dysphagia.
    - Schedule varies but repeating procedure every 1–2wk, with no more than 3 step dilatations on any occasion, advised.
    - More than 50% need repeat dilatation: risk factors are number of previous dilatations and persistent oesophagitis.
- Maintenance → PROTON PUMP INHIBITORS advised.
- For strictures refractory to endoscopic treatment, some evidence supporting intralesional steroid injection, using triamcinolone.
- Emerging data on biodegradable stents.
- For patients undergoing large endoscopic mucosal resection, evidence supporting administration of prednisolone following procedure ↓ stricture formation.

Risks of dilatation

- Perforation (<0.5% for benign strictures, 2–6% for malignant strictures).
- Bleeding (<0.5%).
- Bacteraemia uncommon and antibiotic prophylaxis only indicated in immunocompromised (see ➢ 'Antibiotic prophylaxis', p. 198).

Oesophageal tumours

Classified into epithelial or non-epithelial, benign, or malignant (Table 4.28).

Table 4.28 Classification of oesophageal tumours

Epithelial	Non-epithelial
Malignant	
Squamous cell carcinoma	Lymphoma
Adenocarcinoma	Sarcoma
Adenocarcinoma of oesophago-gastric junction	Metastases
Other rare malignancies, e.g. small-cell carcinoma (1–5% of oesophageal cancers)	
Benign	
Papilloma	Leiomyoma
Adenoma	Granular cell tumours
	Others (lipoma, haemangioma)

Malignant epithelial tumours (see Plate 10)

- Mostly primary oesophageal cancers: squamous cell carcinoma (SCC), adenocarcinoma of oesophagus, and adenocarcinoma of oesophago-gastric junction.
- 6th most common lethal cancer worldwide, with SCC the most common subtype. In Western countries, adenocarcinoma has ↑ 6-fold in last 30y so is now more common than SCC. Rise particularly marked for cancers of oesophago-gastric junction.
- Prognosis remains bleak with 5y survival of 16.5%.

Clinical features

- SCC occurs in upper two-thirds of oesophagus; adenocarcinoma in lower third and at oesophago-gastric junction.
- Symptoms include dysphagia and odynophagia, often accompanied by anorexia and weight loss.
- Both cancer types can infiltrate submucosa, but SCC more locally aggressive and can cause vocal cord paralysis due to recurrent laryngeal nerve invasion and ➔ tracheo-oesophageal fistula in 5%.
- Pulmonary, hepatic, brain, and bone metastases occur. Adenocarcinoma less locally invasive, but haematogenous and lymphatic spread to regional and distant lymph nodes, and liver.
- Most patients present with advanced disease because oesophagus has a rich lymphatic supply and lacks serosa, so spread occurs before luminal stenosis causes symptoms. One study demonstrated almost 90% have T3 or T4 disease once symptoms or signs develop.

Diagnosis

- **Blood tests** May reveal ↓ albumin, anaemia (bleeding or chronic disease), and hypercalcaemia due to PTH-related peptide, especially in SCC (15–30% of patients).
- **Radiology** CXR can be helpful in diagnosing pulmonary metastases or lung infiltrates suggestive of oesophago-bronchial fistula. Contrast radiology with barium can confirm fistulation or obstruction. PET-CT and EUS needed for staging.
- **Endoscopy** Allows histological diagnosis, characterization of length and configuration, and opportunity for therapeutic dilatation. Six biopsies needed for ~100% accuracy.

Staging

- Treatment and outcome are stage-dependent (see ➲ tumour staging, and Table 4.30).
  - T1/2, N0, M0 lesions have significant surgical cure rates.
  - T3, N1 potentially curable but do poorly with surgery alone.
  - Patients with local spread into aorta, airway, pleura, and spine, and those with haematogenous spread, should be treated palliatively, although some evidence that those with positive abdominal lymph nodes can undergo curative resection.
- CT is accurate at identifying solid organ metastases but less good for lymph node metastases, especially in chest. MRI has no significant advantage over CT. PET-CT has high sensitivity and specificity for distant metastases, and recommended as part of staging process.

Epidemiology and risks

See Table 4.29.

- EUS **is** probably the most accurate tool for locoregional staging in the hands of an experienced endoscopist; overall accuracy 72–76% for T stage with ↑ accuracy for T3/4 disease over T1/2 disease. Accuracy of N stage depends on node location (85% for coeliac nodes and 80% for other regional nodes). EUS for guiding FNA improves diagnosis of malignant lymphadenopathy.
- Use of EUS to differentiate between T1a disease (no lymph node involvement and thus endoscopically manageable) and T1b disease (up to 46% lymph node involvement) debated. Some report accuracy up to 82%, while others unable to reproduce, and relies on histological analysis following endoscopic resection (see next).

Treatment

Primary treatment

- Outlined in Table 4.30. Options include surgery alone, chemoradiotherapy, and endoscopic mucosal resection.
- Operative mortality significant. National Oesophago-Gastric Cancer Audit (NOGCA) statistics show 2.4% 30d, and 4.4% 90d, mortality. Surgical approach either transhiatal or involves thoracotomy.
- Squamous cell tumours more sensitive to radiotherapy than adenocarcinomas, but even in SCC combined chemo- and radiotherapy more effective than radiotherapy alone. Results suggest 75% local control rate, with 18% survival at 5y for stage I/II patients.

Table 4.29 Epidemiology and biology of oesophageal cancer

Squamous cell cancer	Adenocarcinoma
Incidence	
Varies by region. Most common in China, Iran, Turkey, N. Africa. More common in men in 6th and 7th decades	More common in white men
Environmental risk factors	
Nitrosamines in diet, exposure to hydrocarbons from cooking in confined spaces, and chewing of betel nuts have been implicated. Alcohol and tobacco both linked to SCC, as well as higher temperature drinks	Apparent inverse relation with ➔ *H. pylori*. Also linked with obesity and tobacco
High-risk diseases	
• ➔ Achalasia (possible due to prolonged stasis of oesophageal contents) • ➔ Caustic strictures • ➔ Coeliac disease	Gastro-oesophageal reflux and ➔ Barrett's oesophagus associated, with most cancers arising from areas of intestinal metaplasia. Annual incidence of cancer in non-dysplastic Barrett's oesophagus 0.5–1%
➔ Plummer–Vinsen/Patterson–Kelly syndrome	
➔ Tylosis	
Concurrent or previous head and neck SCC	
Human papilloma virus (particularly type 16)	
Biology	
Associated oncogenes include cyclin D1	P53 and E-cadherin both important tumour suppressor genes

Table 4.30 Treatment of oesophageal cancer related to TNM classification

T	N	M	Comments
T1a	N0	M0	Endoscopic therapy 1st line although surgical resection offered depending on patient choice
T1b	N0	M0	Surgical resection, although endoscopic resection can be performed for submucosal disease without lymphovascular invasion
T1b T2 T3 T4a	Any N	M0	Surgical resection ± preoperative chemoradio therapyChemoradiotherapy for those unable to have or decline surgery
T4b	Any N	M0	Chemoradiotherapy
Any T	Any N	M1	Palliative therapy

Endoscopic mucosal resection

- Allows accurate staging and histological diagnosis of high-grade dysplasia or carcinoma. Demonstrates depth of invasion, including those limited to mucosa or superficial submucosal layer (sm1), and lymphovascular involvement.
- Endoscopic resection performed using electrocautery techniques, with variability on use of submucosal saline injection prior to resection. Data for outcomes following endoscopic therapy for intramucosal and even superficial submucosal disease (sm1) good, with endoscopic therapy being preferred option. Factors for surgery being preferred over endoscopic therapy in these cases include poorly differentiated tumours and lymphovascular invasion.

Palliative treatment

Includes radio- and chemotherapy, intraluminal brachytherapy, endoscopic dilatation or stent placement, contact thermal therapy, endoscopic laser therapy, and photodynamic therapy. Argon plasma coagulation does not penetrate deeply enough to give relief of dysphagia, and injection of cytotoxic drugs (although theoretically attractive) has not been standardized or compared with other ablative techniques.

- **Chemotherapy** Objective response rates of 30–50% with platinum-based regimes + fluorouracil, a taxane, or topoisomerase inhibitor.
- **Endoscopic therapy** aims at palliating dysphagia, although bleeding and oesophago-respiratory fistulae can also be treated. Endoscopic dilatation can be done using ➲ bougies or TTS balloons. Advantages include simplicity, low cost, and relative safety. Disadvantages include short duration of efficacy and frequent need for repeat procedures. Insufficient palliation for most patients. Best results using thermal ablation obtained with endoscopic lasers; Nd:YAG most common wavelength (see ➢ 'Laser therapy and the GI tract', p. 220).
- Endoscopic stents offer good palliation of malignant strictures and tracheo-oesophageal fistulae. Self-expanding metallic stents have replaced rigid plastic stents as easier to place, give better palliation, and associated with fewer complications.

Prognosis

- Currently, survival is 42% at 1y, and 14% at 5y.
- Relationship with TNM staging complex, as nodal involvement makes huge difference (for example, T3N0M0 disease has higher survival than T1N1M0).

Other oesophageal tumours

- **Malignant non-epithelial tumours** Oesophagus is a rare site of primary lymphoma and sarcoma. Leiomyosarcomas most common. Diagnosis can be difficult with conventional biopsy; EUS-guided FNA is the optimal modality.

- **Benign tumours** Leiomyomas arise from smooth muscle. Subsumed into category of gastrointestinal stromal tumours (➔ GIST). Risk of malignant transformation into sarcomas ↑ with size >5cm diameter. EUS most accurate diagnostic modality. Surgery should be considered if symptoms, uncertainty about diagnosis, or suspicion of malignant transformation. Other benign tumours include granular cell tumours, fibrovascular polyps or hamartomas, and lipomas.
- Recent literature suggests papillomas, previously thought to harbour no malignant potential, may ↑ risk of SCC. Some centres now advocate removal, although data on this are limited.

Oesophagitis

- Most commonly due to gastro-oesophageal reflux (see ► Approach to dyspepsia and gastro-oesophageal reflux), but remember other causes (Box 4.57).
- Diagnostic evaluation usually by endoscopy, although only 30–40% patients with GORD have endoscopically obvious inflammation.
- Most common classification is Los Angeles grading system (Box 4.58).

Box 4.57 Causes of oesophagitis

- Infections: fungal (*Candida*, *Aspergillus*), bacterial (staphylococcus, streptococcus), and viral.
- Systemic diseases: pemphigus, ➔ Behçet's disease.
- ➔ Graft-versus-host disease.
- IBD: oesophagus rarely affected in ➔ Crohn's disease.
- ➔ Drug-induced oesophagitis.
- Chemo- and radiotherapy: mucositis can affect oesophageal mucosa. Radiation above 30Gy associated with oesophagitis. Chemotherapy potentiates radiation-induced oesophagitis.

Box 4.58 Los Angeles grading system for oesophagitis

- Grade A: ≥1 mucosal breaks <5mm long that do not extend between tops of 2 mucosal folds.
- Grade B: ≥1 mucosal breaks >5 mm long that do not extend between tops of 2 mucosal folds.
- Grade C: ≥1 mucosal breaks that are continuous between tops of ≥2 mucosal folds but involve <75% circumference.
- Grade D: ≥1 mucosal breaks that involve ≥75% oesophageal circumference.

Note that Los Angeles system does not describe strictures, hiatus hernias, or Barrett's oesophagus. These have to be described separately.

Ogilvie's syndrome (acute pseudo-obstruction)

Acute pseudo-obstruction localized to colon. Defined as acute colonic dilatation in the absence of an obstructive lesion, usually involving the caecum and right hemicolon. Typically occurs in hospitalized or institutionalized patients. Can be precipitated by trauma, surgery, sepsis, or electrolyte disturbances (such as hypokalaemia). Precise cause not known though dysfunction of autonomic nervous system suggested. Risk of colonic ischaemia and perforation.

Diagnosis

Diagnosis by AXR, which shows gaseous distension of colon, and no bowel sounds on examination. Risk of colonic perforation is ↑ when caecal diameter >10–12cm, and if distension present >6d. CT helpful in identifying alternative causes of intestinal obstruction.

Treatment

- NBM, NG tube and IV fluids.
- Treat any precipitating factors.
- Water-soluble contrast examination to exclude mechanical obstruction: hyperosmolarity often also helps evacuate colon. Contrast examination should not be performed if possible perforation.
- Try and decompress colon with rectal decompression tube.
- Neostigmine (2.5mg IV over 1–3min) can be very helpful: patients should be on cardiac monitor and have IV atropine available in case of bradycardia. Response usually within 20min. Treatment can be repeated up to three times until successful.
- Surgery advisable for patients with caecal diameter >12cm who are refractory to medical or endoscopic management. Tube caecostomy can be helpful. For patients with fever, leukocytosis, or peritoneal signs, right hemicolectomy may be required.

Opioid dependence

Potent analgesics, extremely effective for acute pain and chronic cancer pain. Although widely used, far less evidence for efficacy in chronic non-cancer pain, and liable to cause dependence ± abuse. Other patients use opioids (particularly heroin) recreationally. Misuse associated with significant morbidity and mortality, as well as social, family, and occupational impacts, and legal consequences.

Non-cancer chronic pain is prevalent, debilitating, and complex to manage. Opioids prescribed in this context are widely diverted and improperly used.[2] Many GI conditions are associated with chronic pain, and while opioids may have been started in good faith, dependence becomes problematic, as can side effects including constipation and withdrawal (which can both compound abdominal discomfort).

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[2] Volkow ND & McLellan AT (2016). *N Engl J Med* **374**: 1253–63.

Dependence has occurred when the patient takes drugs in greater doses or for longer duration than intended, and spends time trying to obtain, use, or recover from them. Addiction is defined as cravings, compulsive use, and a strong tendency to relapse after withdrawal. However, these rarely develop in patients treated for cancer pain, where ↑ requirements tend to reflect ↑ pain levels.

Opioid intoxication

Clinical features

Drowsiness, pupillary constriction, slurred speech, respiratory depression, hypotension, and coma.

Management

- Protect airway. Support oxygenation and ventilation as necessary.
- Remove source of opioid if ongoing (infusion, patches).
- If RR<8/min and not maintaining airway/oxygen saturations, give bolus naloxone 200μg IV (use IM route if IV not immediately available). Repeat dose every 2min if no response, or response transient, up to maximum of 2mg.
- Aim for reversal of respiratory depression (not GCS) with adequate oxygen saturations for minimum of 15min.
- Naloxone has shorter half-life than most opioids, hence respiratory depression can reoccur rapidly following bolus doses. If this is likely, initiate naloxone infusion (prescribe 60% of naloxone dose required to maintain reversal for 15min to run over 1h IV).

Opioid withdrawal

Clinical features

- Autonomic: diarrhoea, vomiting, diaphoresis.
- CNS excitation: insomnolence, agitation, tremor.
- Pain: abdominal cramps, myalgia.
- Craving.
- High rates of comorbid psychiatric illness or co-drug abuse (especially cocaine, cannabis, alcohol, and sedatives).

Management

- Recognize and acknowledge opioid use as problem.
- Drug substitution:
  - Opioids with rapid onset and short half-life have greatest potential for abuse. Although often appropriate for severe acute pain, IV preparations particularly prone to leading to misuse in patients with chronic pain syndromes.
  - Longer acting opioids can address cravings without requiring destructive ± criminal behaviours associated with recreational use.
  - 1st line usually methadone. Additional side effect beyond those of other opioids is ↑ QT interval on ECG.
  - 2nd line buprenorphine. Partial agonist, therefore limits maximum amount of opioid. Safer in overdose, but for same reason ceiling effect may not be suitable for initial therapy if addicted to very high doses of opioid.

  - Management of acute pain in patients on substitution therapy is challenging. Although both methadone and buprenorphine are potent analgesics, these properties last 4–8h (although dosed every 24–48h). Although there may be concern that use of other opioids may cause addiction relapse, little evidence that exposure during acute pain ↑ rate (and some suggestion stress of unrelieved pain could be more likely to trigger relapse). Useful to have expert guidance, and if supplemental opioids are required best prescribed scheduled rather than prn.
- Substitution therapy most effective alongside psychological therapies (behavioural, community support, contingency management, cognitive behaviour therapy).

! Pitfall. Diagnostic overshadowing

Drug misuse or withdrawal can mimic presentations of other serious pathologies. There is a risk of missing the true diagnosis in these patients, particularly when both coexist.

Optical biopsy

Encompasses several techniques using light to enhance detection of dysplastic lesions, most commonly (at time of writing) in upper GI tract, although emerging data within colon. Broadly, includes number of techniques including confocal laser endomicroscopy (CLE), spectroscopic techniques, and optical coherence tomography.

- CLE provides real-time histological assessment through high-resolution imaging. Relies upon fluorescent dye, most commonly injected fluorescein, prior to laser illumination. Trials include probe-based and endoscopic-based format.
- Spectroscopy includes fluorescence spectroscopy (± exogenous fluorescent agents with affinity for neoplastic tissues), elastic scattering spectroscopy, and Raman spectroscopy. Techniques not yet optimized for clinical use.
- Optical coherence tomography analogous to US but uses light waves to produce cross-sectional images. As with spectroscopy, evolving technique. Further refinements anticipated that will ↑ accuracy for detecting pre-neoplastic lesions.

Oral contraceptive pill (OCP)

OCPs, particularly those containing higher doses of oestrogens, associated with a range of GI conditions.

- Hepatic adenomas are benign liver tumours, clearly associated with OCPs (risk 3–4/100,000 exposed ♀). Complications include pain (due to size) and rupture. May disappear after stopping OCP.

- Cholestasis due to OCPs similar to ➲ intrahepatic cholestasis of pregnancy (and occurs on taking OCPs in 50% of ♀ who experienced condition in pregnancy). May be dose-dependent oestrogen effect on bile secretion. Appears <6mo after starting OCPs.
- ➲ Focal nodular hyperplasia probably not caused by OCPs, but drug may promote growth and risk of rupture.
- ➲ Hepatocellular carcinoma very rare in patients on OCPs, but risk may be ↑ in those using OCPs for >8y.
- Risk of ➲ Budd–Chiari syndrome doubled. ➲ Portal vein thrombosis reported, usually in conjunction with other prothrombotic tendency.
- ➲ Intestinal ischaemia reported in patients with blood group A.
- Association between oestrogen-containing OCP use and ➲ Crohn's disease (relative risk 1.46).[3] Does not mandate discontinuation, but consider progesterone-only pill or alternative methods of contraception in ♀ with refractory disease.

In contrast with detrimental effects, OCPs have also been used therapeutically to treat recurrent blood loss due to ➲ angiodysplasia.[4]

Oral rehydration solution (ORS)

- Can be life-saving in children with diarrhoeal illness. Also helpful for patients with high-output stomas and ➲ short-bowel syndrome.
- Principle is to stimulate sodium and water absorption by sodium glucose co-transporter in intestinal epithelial brush border. Glucose enhances sodium absorption by active carrier process; water follows passively. Rehydration solutions for treating severe diarrhoea should contain alkalinizing agent to counter acidosis, and be slightly hypo-osmolar (about 250mOsm/L) to prevent osmotic diarrhoea.
- Precise composition controversial (Table 4.31). Debate about type of carbohydrate that should be used and optimal concentrations of sodium, potassium, chloride, and base (Cochrane review, 2011 🔗 http://www.cochrane.org/CD003754/INFECTN_oral-rehydration-salt-solutions-for-treating-cholera-lower-salt-content-versus-higher-salt-content-solutions).

Table 4.31 Composition of oral rehydration solutions

Solution	Na (mM)	K (mM)	Cl (mM)	Citrate (mM)	Glucose (mM)	Osmolarity (mOsm/L)
WHO	75	20	65	10	75	245
UK formulation	60	20	50	10	90	~300

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[3] Khalili H (2016). *Drug Saf* **39**: 193–7.

[4] Hodgson H (2002). *Lancet* **359**: 1630–1.

Components

- Glucose is the most commonly used substrate and should be provided at 70–150mM; higher concentrations cause osmotic diarrhoea. Replacing glucose with polymeric carbohydrate such as rice syrup solids provides a hypotonic solution that is better at ↓ stool output.
- In developed countries, ORS contains lower concentrations of sodium (50–60mM) than WHO formulation (75mM), as patients tend to suffer less severe sodium loss. Stool sodium concentration in ➲ cholera ≈90mM; maximum absorption of sodium occurs at concentration of 120mM and this higher concentration may be optimal in patients with ➲ short-bowel syndrome and high stoma output.
- Potassium concentration in ORS ≈20mM, although stool potassium concentrations often higher; 30–35mM may be more appropriate.

Osler–Weber–Rendu syndrome

See: ➲ Hereditary haemorrhagic telangiectasia.

Osteoporosis and metabolic bone disease

See also: ▹ 'Bone densitometry' (p. 167).

Definitions

- **Osteoporosis** Condition of ↓ bone strength, conferring risk of fracture. Defined as T-score >2.5 SD below average, where T-score compares bone mineral density (BMD) with controls at peak BMD (i.e. young fit adults). Z-score matches for age and sex.
- **Osteopenia** Less severe reduction in BMD (–1 to –2.5. SD), but affects >15% of young ♀, and 40% of ♀ aged >50y.
- **Osteomalacia** Defective mineralization due to vitamin D deficiency.

At-risk groups in gastroenterology/hepatology[5]

- Chronic cholestatic liver disease (e.g. ➲ primary biliary cholangitis and ➲ primary sclerosing cholangitis): 20% of patients with primary biliary cholangitis (PBC) have osteoporosis at time of referral, and 50% have severe bone loss at time of ➲ liver transplantation. All patients with cirrhosis are at risk.
- ➲ Coeliac disease: osteoporosis in 5–10%, and osteomalacia in association with vitamin D deficiency.
- Inflammatory bowel disease (➲ Crohn's disease and ➲ ulcerative colitis): malnutrition and bowel resection may predispose to osteoporosis, but long-term steroid therapy main reason for ↓ BMD, with 40% ↑ in fracture risk over controls.
- Post-gastrectomy: calcium and vitamin D malabsorption contribute to osteomalacia in 10–20%, osteoporosis in >30% >10y post-surgery.
- ➲ Chronic pancreatitis: malabsorption of fat-soluble vitamins.
- Long-term steroid use.
- Any cause of ➲ body mass index (BMI) <19, or physical inactivity.

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[5] Compston J *et al.* (2013). *Maturitas* **75**: 392–6.

Investigation

- Bloods:
  - Serum calcium: usually normal in osteoporosis.
  - Parathyroid hormone (PTH): ↑ PTH, with ↓ phosphate, and normal/ ↓ calcium suggests secondary hyperparathyroidism, vitamin D deficiency, and osteomalacia.
  - 25-(OH) vitamin D: deficiency often dietary, contributing to osteomalacia.
  - LFTs: ↑ ALP in presence of normal γGT suggests ALP of bone origin (e.g. in osteomalacia). ALP isoenzymes can be performed to differentiate bone from liver.
  - Thyroid function tests.
- Plain X-rays: osteopaenia may be visible on plain X-rays, but only after 30–40% bone loss has occurred.
- Bone densitometry: most accurately assessed using dual energy X-ray absorptiometry (DEXA), usually of femoral neck and lumbar spine. If steroid use is planned (e.g. prednisolone 7.5mg/d for >3mo) baseline and follow-up DEXA in 6–12mo should be performed. Spine measurements unreliable in elderly because of presence of osteophytes, extraskeletal calcification, and spinal deformity.

Management

- Correct calcium and vitamin D if deficient (e.g. calcium carbonate 1–1.5g/d and see ➲ vitamin D). Role of supplementation in patients who are replete controversial as calcium supplementation potentially associated with cardiovascular adverse effects. Prudent approach at present may be to ↑ dietary calcium intake and use vitamin D alone.
- Bisphosphonates 1st line specific therapy for osteoporosis. Low cost supports alendronic acid 70mg/wk as initial choice.
  - Options for patients intolerant or with contraindications to alendronic acid include risedronate, zoledronic acid, denosumab, or raloxifene. Review treatment after 3y.
  - HRT useful in postmenopausal ♀.
- Avoid smoking and excess alcohol.
- In chronic liver disease, ➲ liver transplantation associated with further reduction in BMD over first year, then improvement.

Guideline

🖱 UK National Osteoporosis Guideline Group on diagnosis and management of osteoporosis in postmenopausal women and older men (2013).

Overlap syndromes

Clinical scenario where ➲ autoimmune hepatitis (AIH) coexists with another immune-mediated disease, particularly ➲ primary biliary cholangitis (PBC) or ➲ primary sclerosing cholangitis (PSC). More common in younger patients.

- **AIH/PBC overlap** Positive anti-AMA Ab occur in 10% of patients with AIH. AIH/PBC overlap syndrome should be considered when compatible liver biochemistry (ALT or AST 5× ULN), histology, and positive antibodies present. → URSODEOXYCHOLIC ACID (UDCA) usually given (12–15mg/kg/d) in addition to steroids and → AZATHIOPRINE in those with prominent AIH features.
- **AIH/PSC overlap** Mainly reported in children/young adults. Cholangiogram (MRCP/ERCP), histology, biochemical, and serological markers show features of both conditions. Also known as autoimmune sclerosing cholangitis. Treat with → CORTICOSTEROIDS ± → AZATHIOPRINE + → URSODEOXYCHOLIC ACID. 2nd line agents include mycophenolate mofetil or tacrolimus. More aggressive disease course compared to AIH alone.
- **AIH/➲ hepatitis C** Characterized by chronic HCV infection with anti-LKM-1, ANA, SMA Abs, and ↑ serum IgG. Treatment was historically difficult, as → INTERFERON could worsen AIH associated liver disease while immunosuppression for AIH could ↑ HCV replication. Relevance now ↓ with advent of direct acting antivirals.

Oxalate stones

Dietary oxalate (found in tea, chocolate, cola, vegetables) usually precipitated as calcium oxalate in bowel and lost in stool. In conditions with ➲ bile acid malabsorption (e.g. ➲ short-bowel syndrome, terminal ileal ➲ Crohn's disease), unabsorbed long-chain fatty acids compete with oxalate for available calcium. As result, ↑ amounts of free oxalate reach the colon, are absorbed, and ultimately excreted by the kidney. Hyperoxaluria then predisposes to calcium oxalate kidney stones (>20% of patients with short-bowel syndrome).[6] Urinary oxalate should be measured in at-risk patients. No risk if colon is removed too.

Management

- Maintain adequate fluid intake, and ↓ fat intake.
- Restrict high oxalate foods (for example, guide patients to Harvard School of Public Health list https://regepi.bwh.harvard.edu/health/Oxalate/files).
- If hyperoxaluria continues:
  - Oral calcium with large meals (binds luminal oxalate).
  - Potassium citrate mixture (30%/5%) 10ml PO tds, well-diluted in water, alkalinizes urine and reduces risk of stones. GI side effects can occur (abdominal discomfort, diarrhoea), and monitoring of serum electrolytes and creatinine recommended.

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[6] Morgan MSC & Pearle MS (2016). *BMJ* **352**: i52.

P

Paget’s disease: see ➲ Anal cancer *486*
Pancreas divisum *486*
Pancreatic cancer *487*
Pancreatic cystic tumours *489*
Pancreatic endocrine tumours (PETs) *490*
Pancreatic function tests: see ➢ ‘Pancreatic function tests’ (p. 153) *492*
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Pyoderma gangrenosum *527*

Paget's disease

See: ➔ Anal cancer.

Pancreas divisum

- In embryonic development, dorsal and ventral pancreatic buds join so that body and tail of pancreas drain predominantly through major papilla (with common bile duct) via ventral pancreas. In 4% of population, ventral duct not linked to dorsal duct, which then drains through smaller accessory duct (duct of Santorini) (Fig. 4.16).
- May be cause of recurrent ➔ acute or ➔ chronic pancreatitis, and accessory sphincterotomy/sphincteroplasty may improve symptoms. However, aetiological link controversial, as minimally ↑ prevalence of pancreatitis in patients with pancreas divisum (estimated <5% will ever present with complications).
- Can be seen at ▷ ERCP, or with secretin-enhanced ▷ MRCP.

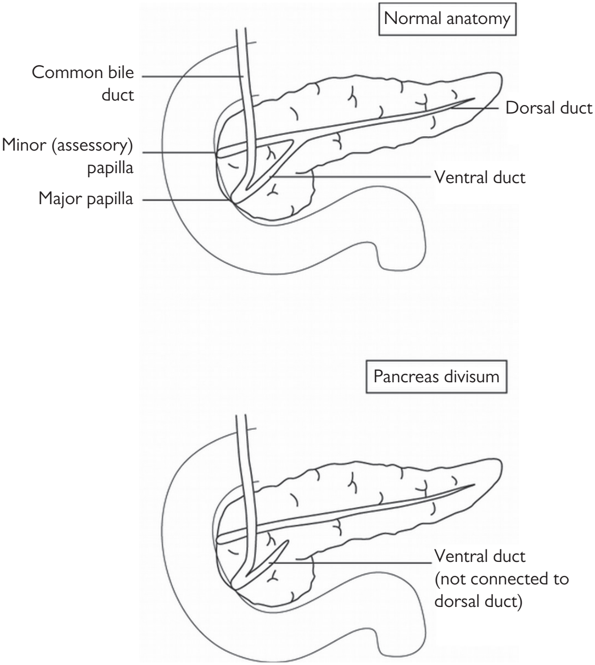
Normal anatomy
Common bile duct
Minor (assessory) papilla
Major papilla
Dorsal duct
Ventral duct
Pancreas divisum
Ventral duct (not connected to dorsal duct)

Fig. 4.16 Anatomical arrangement of pancreatic ducts.

Top: most common arrangement, where pancreatic secretions empty with bile through major duodenal papilla. In ≈70% of adults, proximal portion of dorsal duct remains patent and some pancreatic secretions empty through accessory papilla. Bottom: pancreas divisum, where embryonic dorsal and ventral ducts fail to fuse, and 80–95% of secretions empty from dorsal duct through accessory papilla.

Pancreatic cancer

Epidemiology

- 4th leading cause of cancer death in USA and Europe (incidence ~10/100,000). Median age at diagnosis 65y. More common in ♂.
- No clear cause in most cases, but risk factors include ➲ chronic pancreatitis and smoking. 8% of patients with pancreatic cancer have 1st-degree relative with disease, related to both underlying ➲ hereditary pancreatitis (40% risk by age 70y) and familial pancreatic cancer. Also links with some hereditary breast cancers.
- Onset of diabetes within previous 2y in patients without family history of diabetes also linked.

Pathogenesis

- Ductal adenocarcinoma accounts for 90% of tumours (others include ➲ pancreatic cystic tumours and ➲ pancreatic endocrine tumours).
- Mutations within *KRAS2* and *CDKN2* in >90% of cancers.
- 75% in pancreatic head, 10–15% in body, and 5–10% in tail.
- Metastases to regional lymph nodes, liver, and occasionally lung.

Clinical features

- Jaundice (at presentation in 50%), weight loss (85%), anorexia, and upper abdominal pain radiating to back are classic symptoms. Symptoms of ➲ pancreatic insufficiency occasionally present.
- Nausea and vomiting may relate to duodenal obstruction.
- Palpable gallbladder in 15–30% (Courvoisier's sign—see Box 4.59).
- Migratory thrombophlebitis (Trousseau sign) and venous thrombosis (including ➲ portal vein thrombosis) occur at ↑ frequency.
- Differential diagnosis includes distal ➲ cholangiocarcinoma, ➲ ampullary cancer, focal pancreatitis in head of pancreas, and (rarely) ➲ autoimmune pancreatitis/IgG4-related pancreatitis (Box 4.60).

Box 4.59 Courvoisier's law

'Jaundice in the presence of a palpable gallbladder is not explained by gallstone obstruction of the bile duct.'

Ludwig Georg Courvoisier, Swiss surgeon 1843–1918

Probably explained by slow onset of biliary dilatation with distal bile duct tumours and thin walled uninflamed gallbladder (in contrast to chronically inflamed gallbladder in stone disease, which dilates less easily). Exceptions to rule include ➲ gallbladder empyema with cystic duct stone obstruction and ➲ Mirizzi's syndrome.

Box 4.60 Differential diagnosis of pancreatic mass

- ➲ Pancreatic cancer (ductal adenocarcinoma).
- Distal ➲ cholangiocarcinoma.
- ➲ Ampullary cancer.
- ➲ Lymphoma.
- ➲ TB.
- ➲ Pancreatic endocrine tumour.
- ➲ Autoimmune pancreatitis.
- ➲ Acute and acute-on ➲ chronic pancreatitis.
- von Hippel–Lindau disease.
- ➲ Pancreatic cystic tumour.
- ➲ Pancreatic pseudocyst.

Investigation

- Aimed at making diagnosis, and tumour staging (see ➲ TNM classification).
- LFTs may show ↑ Bn, ↑ ALP/γGT.
- ↑ Serum CA19–9 in 75–85%, but value >100U/ml only highly specific for malignancy in absence of biliary obstruction. ▷ Carcinoembryonic antigen (CEA) ↑ in 40%, but of little diagnostic use.
- Transabdominal US accurately shows biliary dilatation, but views of pancreas often incomplete. Pancreatic protocol CT defines tumour and size, demonstrates local vascular involvement (portal vein, superior mesenteric artery/vein), retroperitoneal invasion, and liver metastases. Only imaging modality needed to make diagnosis in >90%. Very accurately demonstrates irresectability, but falsely suggests resectability in 25–50% of cases.
- MRI rarely used instead of CT, but has comparable accuracy.
- ERCP allows endoscopic stenting (with plastic stent until histological confirmation of inoperable cancer) and cytological brushings.
- Endoscopic US complements CT staging, and enables tissue diagnosis via fine needle aspiration cytology (FNAC) or biopsy, and useful for 'trouble-shooting' small pancreatic lesions/unexplained strictures.

Management

- Curative resection in <20% (due to late clinical presentation for cancers in body/tail, and frequent local vascular involvement for head lesions) - overall survival at 1y and 5y 20% and 4%, respectively. Although invasion of superior mesenteric or portal vein is no longer an absolute contraindication to resection, surgery is precluded by superior mesenteric, coeliac, or hepatic artery involvement. In those undergoing curative resection (▷ Whipple's procedure: see p. 186), 5y survival 10–25%.
- For locally advanced, non-resectable disease, optimal chemotherapy regimen not established and patients should ideally be enrolled into clinical trial. If ineligible, a gemcitabine-based regimen is preferred. If no progression, can be followed by external beam radiotherapy.

- For advanced disease, most evidence to support FOLFIRINOX regime, although significant toxicity reported. New molecular targeted therapies (e.g. targeting angiogenesis) undergoing trials.
- ➢ Pain control (see p. 135) may be a particular problem, necessitating regular opiates. Radiotherapy and coeliac plexus block may help.
- Bile duct stenting via ERCP or percutaneous transhepatic drain (PTD), increasingly using self-expandable mesh metal stents (SEMS), indicated for patients with obstructive jaundice, especially if surgery is not an option. In patients with non-resectable tumour and duodenal obstruction (5% of patients), surgical biliary bypass or duodenal SEMS are options.

Pancreatic cystic tumours

Background

- Cystic neoplasms of pancreas account for 10–15% of cystic lesions (remainder ➲ pancreatic pseudocysts (80–90%), true cysts and acute fluid collections after acute pancreatitis), and represent only 1% of pancreatic neoplasms.
- Mucinous cystic neoplasm (MCN), serous cystadenoma, and intraductal papillary mucinous tumour (IPMT) (Fig. 4.17) account for >90% of pancreatic cystic neoplasms (Table 4.32).

Clinical features

- Increasingly diagnosed incidentally on abdominal imaging.
- IPMT may be misdiagnosed as idiopathic recurrent or ➲ chronic pancreatitis, with pancreatic duct abnormalities, and ➲ pancreatic insufficiency caused by mucus obstruction of pancreatic duct.
- May occasionally present as for ➲ pancreatic cancer (i.e. weight loss, jaundice, pain).

Investigation

- CT and MRI/MRCP to define cyst architecture and relationship with pancreatic duct.
- EUS allows cyst aspiration and biopsy of nodules or mass lesions.
- Fluid analysis allows differentiation from ➲ pancreatic pseudocyst. ↑ cyst CEA suggests malignancy, but CA19–9 not of use.
- ERCP may demonstrate mucus, either emanating from wide open papilla (pathognomonic of IPMT), or within dilated pancreatic duct.

Management

No standardized protocol. Manage in specialist centres. Increasing cyst size (e.g. >3cm) and wall are nodularity risk factors for malignancy. Need to balance potential cure from surgery against requirement for radical resection (Whipple's procedure or distal pancreatectomy, depending on site) in asymptomatic patients with cystic tumours of low malignant potential.

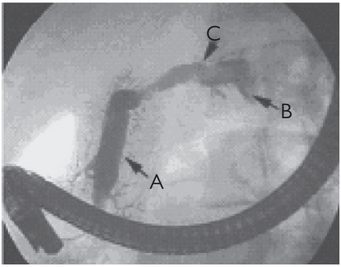

Fig. 4.17 IPMT in tail of pancreas. ERCP shows dilated main pancreatic duct (A), abnormal ducts in tail (B), and filling defects due to mucus (C).

Table 4.32 Pancreatic cystic tumours (most common forms)

	Mucinous cystic neoplasm (MCN)	Serous cystadenoma	Intraductal papillary mucinous tumour (IPMT)
Sex	>80% ♀	>80% ♀	>50% ♀
Peak age	50y	70y	60–70y
Presentation	Mass/pain	Mass/pain	Recurrent pancreatitis
Pancreatic site	Body/tail	Head/body	Head
CT findings	Septae, calcification	Septae, calcification	No septae
Pancreatic duct dilatation	No	No	Yes
Duct–cyst communication	No	No	Yes
Tumour Markers	High CEA Low amylase in cyst fluid	Variable, often low	High amylase in cyst fluid, often low tumour markers
Malignant potential	8–33% of cases	Very rare	15–40%

Pancreatic endocrine tumours (PETs)

- ➔ Neuroendocrine tumours of GI tract classified in two groups: ➔ carcinoid tumours and PETs. Latter (see Table 4.33) arise from pancreatic islet cells.
- Primary insulinomas and glucagonomas occur exclusively in pancreas, but 50–70% of ➔ gastrinomas arise from extrapancreatic sites. May be associated with other conditions, including ➔ multiple endocrine neoplasia type 1 (MEN-1), von Hippel–Lindau disease, neurofibromatosis type 1 (NF-1), and tuberous sclerosis.
- PETs may be functional (associated with clinical syndrome related to hormone release) or non-functional.

Table 4.33 Pancreatic endocrine tumours (PET)

Syndrome	Hormone released	Clinical features	Rate of malignancy (%)	Incidence per million
Gastrinoma (Zollinger–Ellison syndrome)	Gastrin	Recurrent upper GI tract ulceration	70–80	1
Insulinoma	Insulin	Hypoglycaemic episodes Obesity	<10	1–2
Glucagonoma	Glucagon	Weight loss Diarrhoea Dermatitis (migratory necrolytic erythema)	60	0.1
VIPoma	Vasoactive intestinal polypeptide	Watery diarrhoea ↓ K, ↓ Mg^{2+} Flushing	>60	0.5
Somato-statinoma	Somatostatin	Diarrhoea	>70	<0.1

For details on practical aspects of measuring gut hormones, see ▸ 'Gut hormone profile', p. 148.

Insulinoma

- 90% benign. Located throughout pancreas (⅓ head, ⅓ body, ⅓ tail), usually <5cm, with multiple lesions in ~10%. Clinical features relate to symptomatic hypoglycaemia and patients may become morbidly obese due to overeating to avoid.
- As with other functional NETs, diagnosis depends on localizing tumour and demonstrating excess hormone. In >90%, 48h fast with 3–6hrly blood glucose, plasma insulin, and C-peptide levels induces hypoglycaemia and demonstrates disproportionately ↑ insulin. Note in exogenous insulin administration, C-peptide levels <200pmol/L).
- CT/MRI ± PET localizes lesion in <40% if 1–3cm, and EUS, angiography, and selective venous sampling may be required.
- Management includes advice to take small regular meals, and diazoxide (inhibits insulin release); start at 5mg/kg/d PO in 2–3 divided doses and titrate to response. This drug and → OCTREOTIDE control symptoms in 60%. Surgery provides complete cure in 70–95%.

Glucagonoma

- Glucagon stimulates glycogenolysis and insulin secretion, and inhibits pancreatic and gastric secretion and gut motility. Association with ➲ MEN-1 in 20%. Metastases/local invasion in 50–80%.
- Usually >5cm, secrete excess glucagon, causing dermatitis (migratory necrolytic erythema), weight loss, glucose intolerance, and anaemia. Hyperglycaemia in 40–90%.
- Diagnosis made on demonstrating ↑ plasma glucagon >1,000pg/mL (normal <200pg/mL). Treatment includes diabetes control and use of → OCTREOTIDE (may improve weight loss, diarrhoea, and rash).
- Surgery performed for local disease, but cure in only 20%.
- 70–80% malignant, with 5y survival 50%.

VIPoma (Werner–Morrison syndrome)

- Usually solitary tumours in tail of pancreas.
- Characterized by profound watery diarrhoea, dehydration, hypokalaemia, hypochlorhydria, hypercalcaemia and metabolic acidosis.
- Diagnosis made on basis of large-volume diarrhoea (>3L/d in >75% of patients) and ↑ serum VIP levels.
- Medical management includes careful fluid and electrolyte replacement. May need >5L fluid and 350mEq potassium/d). → OCTREOTIDE controls symptoms, but effect may be short-lived. Surgery completely relieves symptoms in ≈30%.
- 50% have metastasis at presentation.

Non-functional PETs

Non-functional PETs (⅓ of PETs) usually occur in pancreatic head and generally larger than functional PETs. 60–90% malignant.

Pancreatic function tests

See: ⊳ 'Pancreatic function tests', p. 153.

Pancreatic insufficiency

Clinical exocrine insufficiency only occurs when >90% of exocrine pancreas function lost.

Causes

Include ➲ chronic pancreatitis, pancreatic resection (see ⊳ Whipple's procedure, p. 186), and ➲ cystic fibrosis.

Clinical features

- Relate to malabsorption and include steatorrhoea (pale loose/bulky stools often described as oily and difficult to flush), weight loss, abdominal bloating, and discomfort.
- Malabsorption of fat-soluble vitamins (see ➲ vitamins A, ➲ D, ➲ E, ➲ K) may give rise to range of clinical problems, including metabolic bone disease (see ➲ osteoporosis).
- In chronic pancreatitis and significant exocrine insufficiency, pain often absent, reflecting loss of functioning pancreas.

Diagnosis

Confirmed using ➢ faecal elastase and ➢ pancreatic function tests (see p. 153). Significant exocrine insufficiency unusual in absence of structural abnormality of pancreas (e.g. pancreatic atrophy, calcification, pancreatic duct abnormalities).

Management

Includes treating underlying cause, → PANCREATIC ENZYME SUPPLEMENTS, treatment/prevention of ➲ osteoporosis, and replacement of fat-soluble vitamins. See also ▶ Approach to malabsorption and steatorrhoea.

Pancreatic pseudocyst

Background

- Not a true epithelial cyst. Usually represents localized fluid collection (2–30cm). Accounts for 80–90% of pancreatic cystic lesions.
- Arise due to pancreatic duct disruption. Complicates 16–50% of cases of ➲ acute pancreatitis, 20–40% of ➲ chronic pancreatitis, and rarely associated with ➲ pancreatic cancer or trauma. By convention, cyst needs to be present for >4wk after acute pancreatitis to make diagnosis ('acute fluid collection' if <4wk).

Clinical features/complications

May be asymptomatic, or cause symptoms related to:

- Local compression. Biliary obstruction, gastric outlet obstruction.
- Vascular involvement: ➲ portal vein thrombosis, pseudoaneurysm (gastroduodenal/splenic artery involvement). Rapidly ↑ pain, ↓ Hb, or hypovolaemic shock may indicate rupture.
- Infection (in 10%). Usually following rupture. May be associated with development of largely asymptomatic pancreatic ascites, or generalized peritonitis.

Investigations

- Diagnosis usually made with transabdominal US or contrast CT.
- Diagnostic cyst aspiration occasionally needed (via EUS), as high cystic ➲ amylase differentiates from ➲ pancreatic cystic tumours.
- ERCP avoided unless transpapillary drainage considered or diagnosis unclear, as may introduce infection.

Management

- Pancreatic rest (e.g. with NJ feeding) sometimes used in attempt to hasten resolution after episode of ➲ acute pancreatitis but clear evidence lacking.
- Asymptomatic pseudocysts <6cm can be managed conservatively, as most will resolve spontaneously (but may take months).
- Drainage considered for symptomatic pseudocysts >6cm present for >6wk. Reduced role for surgery, and most cases of symptomatic pseudocysts and walled-off pancreatic necrosis (WOPN) managed with minimally invasive approaches to drainage.

  - **Percutaneous drainage** often effective, but may develop cutaneopancreatic fistula if pancreatic duct leak continues, so percutaneous transgastric puncture preferred (allows drainage into stomach after drain removal, or endoscopic internalization of drain).
  - **Therapeutic EUS** Favoured approach to drainage if cyst closely apposed (< 1cm) to stomach/duodenum lumen, as allows detailed cyst delineation, and avoidance of pericystic varices (common in view of ➲ portal vein thrombosis). Cyst drained with plastic 7F diameter pigtail stents or mesh metal lumen apposing stents (LAMs).
  - **Transpapillary drainage** Via ➲ pancreatic stent insertion at ERCP. Depends on cyst–duct communication, and small 5–7F (1.5–2.5mm diameter) plastic stents rarely allow effective drainage.
  - **Surgery** With internal cyst drainage (cyst-jejunostomy) may provide resolution, but 24% complication rate. Persistent or recurrent pseudocysts may ultimately require pancreatic resection if duct rupture does not resolve (▷ Whipple's procedure for cysts in head, distal pancreatectomy if in tail).
- Pseudoaneurysm treated with angiographic embolization; rarely surgery.
- ERCP and plastic stent insertion for biliary obstruction.

Pancreatic stents

- Insertion of small 3–5F polyethylene stents into main pancreatic duct at ERCP increasingly used to prevent post-ERCP pancreatitis, particularly in high-risk patients (in whom pancreatic stents reported to ↓ ERCP-related pancreatitis from 26% to 7%). Caveat that risk of pancreatitis if stenting attempted but fails is very high.
- 80% of stents fall out within 3wk, but checking X-ray at this time essential, with endoscopic stent removal if still *in situ*.
- Long-term pancreatic duct stenting for relapsing or ➲ chronic pancreatitis not of proven benefit, and may cause further stricturing.
- For prevention of post-ERCP pancreatitis, universal use of rectal non-steroidal anti-inflammatories (NSAIDs) may ↓ need for prophylactic pancreatic stenting except in particularly high-risk scenarios.

Pancreatitis

See: ➲ Acute pancreatitis, ➲ Autoimmune pancreatitis, ➲ Chronic pancreatitis, and ➲ Hereditary pancreatitis.

Paracentesis

See: ▷ 'Paracentesis' (p. 177).

Paracetamol (acetaminophen) overdose

Background

Paracetamol remains the commonest cause of drug overdose, and acute liver failure, in resource-rich countries. Very safe at therapeutic levels (<4g/d) as excreted via conjugation to non-toxic glucuronate and sulphate metabolites. In overdose (particularly >10g), these pathways are saturated and a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), is produced. This can be detoxified through a pathway dependent on glutathione, but once stores of this are exhausted, liver injury ensues. ↑ toxicity associated with chronic alcohol excess, malnutrition, staggered overdose, late presentation (>16h), and concomitant use of drugs that induce CYP450 (see ➲ hepatic drug metabolism).

Clinical features

- Patients may be well, or have nausea/vomiting for first 24h.
- Liver failure, with progressive jaundice, hypoglycaemia, ▲ **hepatic encephalopathy** ▲ (often associated with cerebral oedema), and multiorgan failure develop from ≈48h post-overdose.
- Acute renal failure may occur independent of liver failure.

Investigation

- Plasma paracetamol levels (Fig. 4.18) taken ≥4h post-ingestion predict toxicity (and need for treatment). Note that concurrent infusion of → ACETYLCYSTEINE can cause falsely low level measurements, so not advised to initiate treatment prior to taking 4h level unless liver or kidney injury already evident.
- Baseline FBC, U&Es, LFTs, PT/INR, Glu & pH. Abnormalities in LFTs at presentation suggest overdose >18h previously or pre-existing liver disease.
- miRNA-122 shows promise as an early biomarker of liver injury.[1]

Specific management

- If patient presents within 1h of overdose, administer 50g activated charcoal PO or via NG tube.
- → ACETYLCYSTEINE replenishes glutathione stores and virtually abolishes severe hepatotoxicity if given <12h post-ingestion. May provide benefit even if started up to 36h after overdose.
- Indications for acetylcysteine
  - Serum paracetamol levels above cut-off ≥4h post-ingestion (see Fig. 4.18).
  - Patients presenting >12h post-overdose (unless all blood tests normal and blood paracetamol undetectable).
  - Staggered overdose (cut-off for treatment not well-defined but generally any ingestion >75mg/kg/24h should be treated).
  - Unreliable history or timing uncertain.
  - Evidence of acute liver injury on presentation.
  - Management of IV paracetamol overdose currently ill-defined, but in general acetylcysteine recommended for exposure >75mg/kg/24h.

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[1] Vliegenthart AD *et al.* (2015). *Br J Clin Pharmacol* **80**: 351–62.

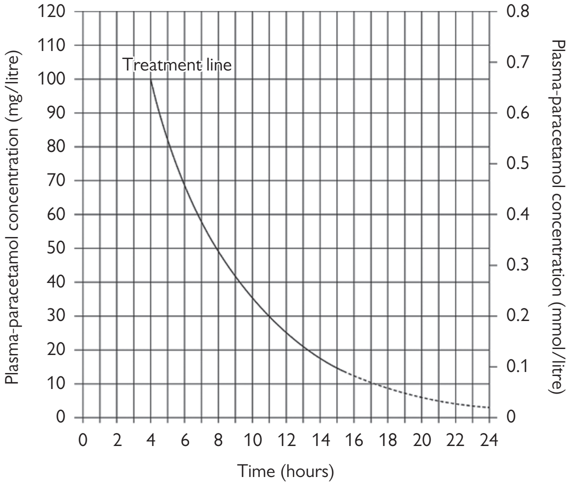

Fig. 4.18 Nomogram for paracetamol overdose.

- Acetylcysteine is provided as 3 consecutive infusions (although alternative regimens such as SNAP protocol being explored). Dosing according to weight bands is associated with lower error rates (see Table 4.34).
- Recheck U&Es, LFTs, INR, and pH after 3rd infusion, and prescribe a further 16h infusion if any of:
  - INR >1.3.
  - ALT >2× ULN, or >2× admission measurement.
  - Deterioration in renal function.
- Continue protracted acetylcysteine infusion until INR ≤1.3 or falling towards normal on 2 consecutive blood tests and <3.

General management

- See also ▲ **Acute liver failure** ▲.
- Daily bloods: FBC, U&Es, LFTs PT/INR, Glu.
- AST/ALT may rise massively (≥10,000U/L not uncommon) at d2–3, but INR/PT and overall clinical state (e.g. ▲ **hepatic encephalopathy** ▲) much more important prognostic markers. If INR normal at 72h significant liver damage will not occur.
- Acetylcysteine itself can cause mild ↑ in INR, but any rise >0.3 above baseline should be assumed to reflect paracetamol toxicity.
- Contact specialist liver unit early, especially if any of following:
  - Arterial pH <7.3.
  - INR >3.
  - Arterial lactate >3mmol/L (following volume resuscitation).
  - Creatinine >200μmol/L.
  - Hypoglycaemia.
  - Any degree of encephalopathy.
- Remains important indication for urgent ➔ liver transplantation.

💣Controversy. Over or undertreatment of paracetamol overdose?

In 2009, the MHRA released updated paracetamol treatment guidelines on the back of a death reviewed by the coroner. Prior to this, the treatment nomogram had two thresholds, one for 'standard' and another for 'high' risk patients. In the new guidance, the 'standard' threshold was abolished, leading to a marked ↑ in numbers of patients admitted and treated with acetylcysteine. Some have argued that this is considerable overtreatment of cases at substantial cost, especially as other countries have higher thresholds but no proportional excess in death or liver transplantation. Consequently much effort has recently gone into identifying better biomarkers of adverse outcomes to refine the patient population who will benefit from treatment, as well as novel protocols that abbreviate duration of acetylcysteine administration (of which one, the SNAP protocol,[2] currently being trialled in some centres in UK).

Guideline

BNF protocol for management of paracetamol overdose (2016).

Table 4.34 IV acetylcysteine dosing (use 200mg/ml solution)

Weight	1st infusion over 1h made up to 200ml in 5% glucose*	2nd infusion (over 4h) made up to 500ml in 5% glucose*	3rd infusion (over 16h) made up to 1L in 5% glucose*
40–49kg	34ml	12ml	23ml
50–59kg	42ml	14ml	28ml
60–69kg	49ml	17ml	33ml
70–79kg	57ml	19ml	38ml
80–89kg	64ml	22ml	43ml
90–99kg	72ml	24ml	48ml
100–109kg	79ml	27ml	53ml
≥110kg	83ml (max dose)	28ml (max dose)	55ml (max dose)

*0.9% saline alternative if 5% glucose unsuitable.

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[2] Bateman DN *et al.* (2014). *Lancet* **383**: 697–704.

Parasitic infection

Parasites of GI tract classified into worms or helminths (➔ roundworms, ➔ tapeworms, and ➔ flukes or flatworms) and protozoa (➔ amoebiasis, ➔ giardiasis, ➔ Coccidia, and ➔ trypanosomiasis).

Parenteral nutrition (PN)

Indications

Nutritional support recommended by NICE in cases of malnutrition, or where malnutrition is likely to develop (due to inadequate intake or poor absorptive capacity, high nutrient losses or ↑ nutritional needs from catabolism). PN indicated if support via enteral route inadequate, unsafe, or GI tract non-functional, inaccessible, or perforated. See also ► Approach to nutritional support.

Techniques for delivery

Parenteral feeds can be given through peripheral catheters (including standard venous cannulae or mid-length fine-bore catheters), peripherally inserted central catheters (PICC), or skin-tunnelled central venous catheters ('Hickman lines'). Major limitation to using peripheral catheters is high incidence of thrombophlebitis, related to:

- Osmolality, pH, and lipid content of nutrition solution.
- Catheter characteristics (diameter, composition).
- Infusion protocol.
- Diameter and position of vein and insertion technique.

Incidence of thrombophlebitis can be minimized by following principles outlined in Box 4.61.

Peripherally inserted central catheters

PN can be administered via PICC line once adequate positioning has been confirmed. See Box 4.62 for practical points on PICC placement.

Tunnelled central venous catheters

Use subcutaneous skin tunnel from point on anterior chest wall distant from point of entry of catheter into vein. Indicated when feeding likely to be for >2wk, peripheral access poor, and when feed osmolality >1,000mOsm/L. Optimal tip placement as for PICC (Box 4.62).

Box 4.61 Practical tips in peripheral PN

- Use as large a vein as possible. Avoid standard Venflons, and use fine-bore (22G or 23G) polyurethane catheter.
- Put GTN patch over infusion site.
- Add 500–1,000IU heparin/L of PN solution.
- Add 5mg/L of hydrocortisone.
- Buffer solution to pH 7.4.
- Keep daily infused volume <3.5L. Use infusion pump.
- Use inline 1.2μm filter.
- Provide at least 50% of total energy as lipid: this serves to keep osmolality low.

Box 4.62 Placing a PICC

- Use basilic (medial) vein at antecubital fossa (avoid lateral cephalic vein as joins axillary vein at right angle, which can make further advancement beyond this point very difficult).
- Thrombosis rates much lower if catheter tip in SVC rather than axillary or subclavian vein. Check on CXR that tip no more than 2cm below line joining lower borders of medial ends of clavicles.

Calculating requirements and choosing the feed

In most hospitals, this will be done by dieticians or members of nutrition team. The following principles apply:

Calculate energy requirements

This can be done by calculating basal metabolic rate (available from charts developed by Schofield).[3]

- Add 10% for each degree Celsius ↑ in temperature.
- Adjust for mobility (add 10% if bed-bound, 20% if sitting in chair, 30% if mobile on ward).
- Add up to 600kcal if weight gain required.

Calculate protein requirements

Most hospitalized patients need 0.8–1.5g/kg/d protein. Any catabolic illness, ➲ protein-losing enteropathy, or nephropathy (or dialysis) will ↑ protein requirements. Protein balance can be checked in most patients, if necessary, by calculating urinary nitrogen loss from urinary urea excretion and comparing this with content of prescribed feed.

Consider amount of fat infused

Optimal percentage of calories that should be infused as fat not known, but most complications occur at rates >1kcal/kg/h, so maximum of 0.7kcal/kg/h usually observed (=500–1500ml of 10% lipid solution).

Consider infused carbohydrate

IV carbohydrate, usually glucose, is a vital source of calories that stimulates insulin secretion and ↓ muscle breakdown (↓ hepatic gluconeogenesis, which needs amino acid precursors from skeletal muscle).

Consider parenteral electrolytes, vitamins, and trace elements

- Sodium: provide patient's weight (kg) as baseline and add calculated losses, remembering that bile and small intestinal/ileostomy fluid near isotonic at 150mM.
- Monitor potassium and calcium (5–10mM required/d) and phosphate (10–30mM/d).

Clinical management of patient on PN

- Daily weight. Contributes to assessment of fluid balance.
- Blood glucose may be ↑ if insulin resistance.
- Watch for pyrexia. Any spike may indicate line sepsis. If present, take blood cultures from feeding catheter and peripheral vein. Stop PN until culture results known.
- ❗ Beware overenthusiastic feeding of critically malnourished patients: danger of ➲ refeeding syndrome.

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[3] Schofield WN (1985). *Hum Nutr Clin Nutr* **39** (**Suppl 1**): 5–41.

- PN can be withdrawn once adequate oral or enteral nutrition tolerated and nutritional status stable. Withdrawal should be planned and stepwise with daily review of patient's progress.

Complications of parenteral nutrition

Complications relating to feeding catheters:

- Mechanical damage to veins or local structures (pneumothorax, brachial plexus injury, thoracic duct injury, haemothorax).
- Vascular complications: air embolism, catheter thrombosis, embolic complications including pulmonary emboli.
- Infectious complications. Line sepsis rates should be <3–5%, but this requires meticulous line care.

Complications related to feeding:

- Metabolic: fluid overload, hyperglycaemia, metabolic bone disease, hyperlipidaemia.
- GI complications: abnormal LFTs common (usually cholestatic, but steatohepatitis seen on histology). Acalculous ➲ cholecystitis (5%), ➲ acute pancreatitis, ➲ gallstones (30%), and gallbladder sludge (approaching 100%) also occur and presumably relate to bile stasis in absence of enteral feeding.

Clinical applications of parenteral nutrition

See sections on nutrition in entries on ➲ Crohn's disease, ➲ ulcerative colitis, ➲ short bowel syndrome, and ▲ **hepatic encephalopathy** ▲. PN also has role in management of gastrointestinal fistulae, and ➲ acute pancreatitis.

Guideline

NICE guideline on parenteral nutrition (2006) 🖱 http://www.nice.org.uk/guidance/CG32.

Parkinson's disease and GI tract

(see also ▶ Approach to gastrointestinal problems in elderly patients)

Parkinson's disease can be associated with **swallowing problems** and **constipation**. See also ▶ Approach to gastrointestinal problems in patients elderly.

- **Drooling** results from ↓ swallowing. Correlates with severity of parkinsonism and can be severe. Anticholinergics can dry mouth but may cause confusion. Irradiation of salivary glands effective, as is botulinum toxin type A injection.
- **Dysphagia** occurs in 50%.
  - Oropharyngeal problems arise because of poor tongue control, difficulty in bolus formation, and delayed transit to pharynx. Food retention in pharynx and consequent aspiration common.
  - Oesophageal dysmotility common in manometric studies and there may be incomplete relaxation of lower oesophageal sphincter. L-dopa may help oropharyngeal phase of swallowing but does not always lead to improved swallowing.
- **Heartburn** and documented oesophageal reflux more common.

- **Constipation** common. Results from slow intestinal transit and sometimes outflow due to pelvic floor problems. Can be masked by overflow incontinence. May result from degeneration of myenteric plexus and be aggravated by anticholinergic drugs as well as inadequate intake of fibre and fluids. Suggested management includes osmotic laxatives or secretagogues (e.g. lubiprostone).

Pellagra

Due to poor intake of niacin (➔ vitamin B_3), or ↓ conversion of tryptophan to niacin. Latter requires riboflavin, thiamine and pyridoxine, and inhibited by excess leucine intake. Pellagra is a wasting disease with dermatitis of exposed areas due to photosensitivity. Fatigue, insomnia, and apathy can lead on to hallucinations and psychosis. Widespread mucosal inflammation causes glossitis, stomatitis, vaginitis, and diarrhoea. Can be associated with drugs (isoniazid) or ➔ carcinoid. Treat by replacing nicotinamide: vitamin B CoStrong tablets PO or Pabrinex® IV/IM contain sufficient concentrations at once-daily dosing.

Peptic ulceration

General pathophysiology, treatment, and complications discussed here. For specific guidance see also ➔ gastric ulcers, ➔ duodenal ulcers, and ► Approach to dyspepsia and gastro-oesophageal reflux).

- Includes all acid-related ulceration: gastric ulcers, duodenal ulcers, oesophageal ulcers relating to gastro-oesophageal reflux, and ulcers in Meckel's diverticulum. Textbooks and pathologists differentiate **ulcers** and **erosions** according to whether erode through muscularis mucosae, but this is not useful to clinicians or endoscopists because ulcers diagnosed by morphological or radiological features.
- Before 1980s, peptic ulcer was considered a chronic relapsing disease. Since then, most shown to be related to ➔ *Helicobacter pylori* infection or ➔ NSAID use, and hypersecretory states such as ➔ gastrinoma (Zollinger–Ellison syndrome) accounting for minority.
- Physiological stress (burns, sepsis, multiorgan failure) can cause multiple superficial erosions. Ulcers arising in burns patients are called **Curling's ulcers**, and those in head injury patients **Cushing's ulcers**. Unlike other stress-related peptic injuries, Cushing's ulcers are associated with hypergastrinaemia.

Pathophysiology

- *Disordered mucosal defences*. These include factors protecting epithelium against acid, such as mucus and bicarbonate in unstirred water layer covering cells, as well as tight junctions between epithelial cells and effective mucosal blood flow.
- *Abnormal acid and motility*. Patients with duodenal ulcers are hypersecretors. This may relate to ↑ gastrin stimulated by *Helicobacter pylori* (HP) or by an HP-mediated ↓ in somatostatin secretion. May be high levels of pepsinogen (again related to HP) and possibly abnormal vagal control or disordered motility with resulting ↑ acid delivery to duodenum.

- Gastric ulcers in body or fundus associated with gastric atrophy, chronic ➔ gastritis, and low acid, while antral gastric ulcers and gastric ulcers associated with concomitant duodenal ulcers associated with high acid output.
- ➔ *Helicobacter pylori* (HP) Strong association with both ➔ duodenal ulcer (DU) and ➔ gastric ulcer (GU), but although experimental HP infection produces gastritis that if untreated can progress to gastric atrophy and cancer, only 20% of infected people get peptic ulcers, so ill-understood host and virulence factors must be important. Paradox about HP is why infection in some produces high acid and duodenal ulceration, while in others leads to chronic gastritis, gastric atrophy, and ➔ gastric cancer. Although may relate to different patterns of infection (antral vs. body), more investigation needed.
- *Non-steroidal anti-inflammatory drugs (NSAIDs)*. Damage GI mucosa by direct and systemic effects. Direct damage occurs within minutes of ingestion and can be ↓ by enteric coating or rectal administration. Systemic effects mediated by ↓ mucosal prostaglandin synthesis with consequent effects on secretion of mucus and mucosal blood flow. Ulcers can be shown on endoscopy in 15–30% patients on chronic NSAID therapy. Risk multiplied with concomitant corticosteroid ingestion; also ↑ by previous peptic ulceration, old age, and comorbidity. Some evidence risk also ↑ by concomitant HP infection, but this is controversial.
- *Other drugs*. Peptic ulcers associated with some chemotherapeutic drugs (intra-arterial fluorouracil), potassium chloride tablets, crack cocaine, and bisphosphonates (especially alendronic acid).
- *Hypersecretory conditions*. Suspect in absence of HP or NSAID use, especially if also diarrhoea, complications (perforation or haemorrhage), or if ulceration extends beyond duodenal bulb. Relevant conditions include:
  - ➔ Gastrinoma.
  - ➔ Systemic mastocytosis and myeloproliferative disorders with ↑ basophils. Produce histamine, which can cause acid hypersecretion. DU in 40%.
  - Antral G cell hyperplasia. Usually consequence of HP infection.

Epidemiology

Rare before 19th century. Became more common in early 20th century, but incidence ↓ since 1960s. Hospitalization rates have not changed, probably because older people consume more NSAIDs. For risk factors, see Box 4.63.

Box 4.63 Risk factors for peptic ulceration

- True: ➔ *Helicobacter pylori*, NSAIDs, ➔ gastrinoma, cigarette smoking, associated diseases such as COPD and cirrhosis, probably some genetic factors (e.g. Lewis blood group antigens mediate HP attachment to mucosa).
- False: alcohol in absence of cirrhosis, dietary factors.
- Uncertain: emotional stress, steroids without other risk factors.

Clinical features

Do not attempt to diagnose peptic ulceration by history alone despite classic descriptions of abdominal pain:

- **Gastric ulcer** Pain soon after meals, not relieved by eating. Associated with anorexia and weight loss in 50%.
- **Duodenal ulcer** Pain 2–3h after meals. Often wakes patient in middle of night. Relieved by eating so most patients maintain or ↑ weight.

Pain of peptic ulceration can be mimicked by cancer, pancreatitis, cholecystitis, reflux, and mesenteric angina.

Investigations

See ► Approach to dyspepsia and gastro-oesophageal reflux. Endoscopic examination alone is a poor predictor of malignancy, and gastric ulcers should always be biopsied at re-scope 6–8wk after initial endoscopy if not healed. Take 6 biopsies, which gives 98% sensitivity; adding gastric brushing improves accuracy further. Duodenal ulcers very rarely malignant so follow-up endoscopy to confirm healing not usually required unless unusual features at initial endoscopy.

Treatments

Test for HP; eradicate if present. Ask about NSAID ingestion.

Histamine receptor antagonists

Used by themselves, healing rate for DU 70–80% and for GU 55–65%. Especially useful for ↓ basal acid output at night, although tolerance can develop rapidly. See → H_2 RECEPTOR ANTAGONISTS.

Proton pump inhibitors

Most effective inhibitors of gastric acid and 1st-line therapy. Even patients taking twice-daily proton pump inhibitors (PPI) often experience nocturnal acid breakthrough, which can be helped by nocturnal H_2RA. Once-daily PPI gives DU healing rate of 80–100%, and GU healing rate of 70–85%. For discussion of possible adverse effect of PPIs, see → PROTON PUMP INHIBITORS.

Antacids

Although antacids can heal ulcers in high doses, they are poorly tolerated, and often cause unacceptable GI side effects. See → ANTACIDS.

Other drugs

Both → SUCRALFATE and → BISMUTH can heal ulcers, but infrequently used. The prostaglandin analogue → MISOPROSTOL has similar efficacy to omeprazole for healing NSAID-induced ulcers, but contraindicated in ♀ of childbearing potential.

Surgery

See ⊳ 'gastrectomy', p. 183. Need for surgery to treat uncomplicated peptic ulcers has almost disappeared because of effective drug treatment. Current indications include bleeding from ulcers not responding to endoscopic therapy, perforated ulcers, and gastric outlet obstruction that cannot be relieved by endoscopic dilatation. Operations for duodenal ulceration include patching perforation with tongue of omentum, or removing acid-producing tissue either with antrectomy or vagotomy (usually highly selective vagotomy). Simple division of vagus results in pyloric spasm, so vagotomy needs to be combined with drainage procedure such as pyloroplasty or gastrojejunostomy. Operations for benign gastric ulcers depend partially on site of ulcer: ulcer near oesophageal junction refractory to medical treatment may need subtotal gastrectomy and Roux-en-Y anastomosis.

Refractory peptic ulcers.
See Box 4.64.

Box 4.64 What to do if peptic ulcer not healed after treatment for 8wk with PPI (12wk for ulcers >2cm)

- Check compliance with drug treatment.
- Is there HP infection?
- Is there ongoing and possibly surreptitious NSAID use?
- Smoking? Cigarette smoking delays healing.
- Is there evidence for a hypersecretory condition?
- Is the ulcer peptic? Consider ➔ gastric cancer (very rarely duodenal cancer), infection, cocaine use, and ➔ Crohn's disease.

Complications

Haemorrhage

Use of aggressive anti-secretory therapy reasonable. No benefit in using H_2 receptor antagonists in controlling bleeding or preventing rebleeding. Important study[4] showed that, in patients who received endoscopic treatment to control acute haemorrhage, bolus of 80mg IV omeprazole followed by 8mg/h infusion for 72h ↓ rebleeding rates and hospital stay. See also: ▲ **Acute upper GI bleeding** ▲.

Perforation

Can be life-threatening. Strong association with NSAIDs, smoking (especially in younger patients), and crack cocaine. Diagnose by erect CXR ± CT. Avoid endoscopy, which will exacerbate any leak. Sometimes careful radiological examination with water-soluble contrast will reveal site of perforation. Usual treatment is broad-spectrum antibiotics, surgery to close perforation, and irrigation of peritoneum. Non-operative therapy is rarely appropriate in highly selected patients where the patient well and perforation is sealed; however, **watch these patients very carefully**—operation indicated at 1st sign of deterioration.

Penetration

Posterior DUs can invade pancreas, and GUs can penetrate left lobe of liver. Choledochoduodenal fistulae and gastrocolic fistulae can occur.

Obstruction

Pain, bloating, early satiety, and vomiting after a meal suggestive. Weight loss can be dramatic. Examine for succussion splash. Gastric aspirate of >200ml after overnight fasting is evidence of delayed gastric emptying. Management medical and endoscopic using dilatation in 70% of cases, the remaining 30% needing surgical bypass of gastric outlet obstruction.

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[4] Lau JW *et al.* (2000). *N Engl J Med* **343**: 310–16.

Perianal Crohn's disease

Incidence

Can occur in 5–25% of Crohn's patients. More common with distal disease, occurring in ≈30% of patients with small bowel involvement and 50% with colonic inflammation. Usually presents concurrently with or after intestinal disease, but can precede intestinal manifestations by several years in up to 20% of patients. Risk factors include age <40y, non-Caucasian or Sephardic Jewish ethnicity, and large bowel disease (particularly with rectal involvement).

Spectrum of disease

- Skin lesions include skin tags (possibly from lymphoedema due to lymphatic obstruction), and abscesses (usually linked to fistula).
- Anal canal lesions include fissures, ulcers, and stenosis. Fissures tend to be eccentric rather than midline. Stricture can relate to smooth muscle spasm or extramucosal fibrosis.
- Perianal fistulae. Often accompany perianal abscesses. Classified by Parkes in 1976: see ➲ anorectal fistulae. Rectovaginal fistulation occurs in ≈5–10% ♀ with perianal disease.

Assessment of severity

- Conventional scoring systems, such as the ➲ Crohn's disease activity index correlate poorly with severity. The Perianal Disease Activity Index (PDAI) has been developed and validated by Canadian group.[5]
- If examination painful, examination under anaesthetic (EUA) appropriate. Imaging includes endoanal US (see ▷ 'endoscopic US', p. 212) and MRI. US very useful for characterizing sphincter defects, and MRI for assessing sphincter integrity and defining fistula tract anatomy. Optimal imaging may need to include two modalities.

Treatment

Medical

- Steroids can prevent fistula healing and may lead to abscess formation.
- Antibiotics useful, but metronidazole should not be used for >3mo (risk of neuropathy). Ciprofloxacin has little effect against anaerobes but is of proven use in perianal Crohn's disease.
- Topical → 5-AMINOSALICYLATES can be effective in rectal disease.
- Fissures increasingly treated with pharmacological therapy, including metronidazole, nitrates (GTN), → BOTULINUM TOXIN, and diltiazem.
- Immunomodulators → AZATHIOPRINE/MERCAPTOPURINE heal ~30% of fistulae. → METHOTREXATE probably has similar efficacy.
- Anti-TNF treatment (→ INFLIXIMAB or → ADALIMUMAB) highly effective in treating fistulae. Combination of anti-TNF and thiopurine prolongs effect.

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[5] Irvine EJ *et al.* (1995). *J Clin Gastroenterol* **20**: 27–32.

Surgical

Surgical options range from drainage of abscesses/fistulae to major interventions such as proctocolectomy with stoma formation. Meticulous attention to adequate drainage essential to successful treatment.

- Emergency treatment of sepsis may involve incision of abscess, with antibiotics. Fistulae after drainage often treated by placing ➲ seton, aimed at preventing further abscess formation. An alternative bridging procedure prior to attempts at definitive treatment is stoma formation, as faecal stream diversion is of definite benefit in Crohn's disease.
- Operations for fistulae complex. An obvious concern and principle of surgery is maintenance of faecal continence.

Pernicious anaemia (PA)

Called 'pernicious' as used to be fatal before treatment became available. Classic pernicious anaemia caused by atrophic gastritis, which results in loss of parietal cells and failure to produce sufficient intrinsic factor (IF) to absorb adequate amount of dietary vitamin B_{12} (cobalamin). This results in megaloblastic anaemia. For other disorders that cause cobalamin deficiency, see ➲ vitamin B_{12}.

Aetiology

In adults, usually autoimmune disorder, with antiparietal cell antibodies in 90% (compared to 5% of healthy individuals). Both binding and blocking antibodies to IF also found. Associated with atrophic gastritis and ➲ achlorhydria. In children, aetiology different: usually hereditary problem of cobalamin metabolism or intrinsic factor production. Coexisting iron deficiency common.

Epidemiology

Most cases occur after age 40, although recognized in children (juvenile pernicious anaemia). Prevalence: 1/1,000. ♀:♂ ~2:1. 20–30% have positive family history. Association with other autoimmune disorders: type 1 diabetes, Addison's disease, vitiligo, and thyroid disease.

Diagnosis

- Macrocytic (megaloblastic) anaemia. Pancytopaenia if severe.
- Low plasma vitamin B_{12}.
- ↑ Bn due to haemolysis occasionally reported.
- Autoantibodies: antiparietal cell, anti-intrinsic factor.
- ➢ Schilling test now obsolete.

Therapy

Centres on B_{12} replacement:

- Standard regimen: hydroxocobalamin IM 1mg three times/wk for 2wk, then 1mg every 3mo. Some evidence that giving larger doses orally (1–2mg/d) effective.
- After initial parenteral replacement, most people can be maintained on oral supplementation of 250–1,000μg B_{12}.

Complications

Risk of gastric adenocarcinoma and carcinoids ↑ 2–3-fold, possibly related to hypergastrinaemia ± hypochlorhydria; these cause enterochromaffin cell hyperplasia, hence ↑ incidence of ➲ carcinoid tumours, which respond to antrectomy and are relatively low-grade malignancy. Annual incidence of gastric cancer 0.1–0.5%. No universal consensus on surveillance; some suggest endoscopy with antral and corporal biopsies every 4y.

Peutz–Jeghers syndrome

Named after Peutz (1921) and Jeghers (1949). Hamartomas represent type of ➲ polyp, characterized by glandular epithelium supported by framework of smooth muscle continuous with muscularis mucosae. Usually multiple. Autosomal dominant and involves germline mutation of serine–threonine kinase gene of chromosome 19. Test for *STK11* mutation.

Characteristic mucocutaneous pigmentation that resembles freckles (see Plate 1). Polyps can be anywhere in GI tract, but commonly found in small intestine. High overall risk of cancer (90% by age 65). Risk of ➲ colonic cancer 40%, with similar rates for ➲ gastric cancer and ➲ pancreatic cancer, as well as ↑ risk of breast, uterine, testicular, and lung cancers. Guidelines for screening include colonoscopy from late teens every 3y, upper GI endoscopy every 2y, annual Hb and surveillance of small bowel; annual breast examination or mammogram; and annual pelvic examination.[6]

Pharyngeal pouch (‘Zenker’s diverticulum’)

Epidemiology and pathogenesis

Present in 1% of people aged >70y. Diverticulum develops in area of weakness where fibres of cricopharyngeal sphincter meet oblique fibres of inferior pharyngeal constrictor muscle. Incomplete relaxation of upper oesophageal sphincter may lead to ↑ pharyngeal pressure proximal to this during swallowing, with subsequent herniation.

Clinical features

Dysphagia, regurgitation, cough, aspiration, and halitosis.

Investigation

- Diagnosis usually made by barium swallow.
- Risk with endoscopy of oesophageal rupture, often related to endoscope tip penetrating base of diverticulum.

Management

Traditionally, treatment surgical, with >90% subsequently symptom free, but endoscopic stapling techniques now also effective.

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[6] Syngal S *et al.* (2015). *Am J Gastroenterol* **110**: 223–62.

Plummer–Vinson/Patterson–Kelly syndrome

Characterized by iron-deficiency anaemia; atrophic changes in buccal, glossopharyngeal, and oesophageal mucous membranes; koilonychia; and dysphagia. Dysphagia due to ➲ oesophageal ring/web formed in post-cricoid region. Squamous carcinoma of tongue and post-cricoid region are complications. Most common in middle-aged ♀; rare in ♂. Aetiology unknown.

Pneumatosis coli

Aetiology and pathogenesis

Multiple gas-filled cysts in submucosa and subserosa. Name misleading, as most cases involve small intestine, and only 6% affect colon. Several theories of pathogenesis, with most evidence supporting bacterial aetiology. Pneumatosis can be induced in laboratory animals by injecting gas-forming bacteria into gut wall, and successful treatment with antibiotics has been reported.

Clinical features

Most common around age 60y. No gender difference. Usually asymptomatic but can cause diarrhoea, mucous discharge, rectal bleeding, or constipation. Can lead to mesenteric ischaemia and infarction.

Management

- Symptomatic patients can be treated with combination of high-flow oxygen for several days (minimum 48h), → METRONIDAZOLE for up to 3mo ± elemental diet for 2wk.
- In acutely unwell patients, pH <7.3, ↑ lactate, HCO_3 <20mmol/L, and ↑ amylase predict need for surgical exploration.

Polyarteritis nodosa (PAN) and the GI tract

Epidemiology

Necrotizing vasculitis affecting medium-sized arteries. Incidence: ≈1.6/million. Associated with ➲ hepatitis B infection (although recent classification separates HBV-related cases into distinct disease entity), and these patients have higher risk of GI involvement.[7] Reducing incidence parallels ↓ in HBV after effective vaccination programmes.

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[7] Soowamber M *et al.* (2017). *Nat Rev Gastroenterol Hepatol* **14**: 185–94.

Clinical features

- Systemic features: fever, arthralgia, mononeuritis multiplex (38–72%), and cutaneous lesions (28–58%, including purpura, nodules, and ulcers).
- Hypertension common, secondary to intrarenal artery involvement. Glomerulonephritis not a feature.
- Abdominal symptoms (usually pain) occur in ≈50%, although abnormal mesenteric vessels can be demonstrated in 80%. Vasculopathy can cause GI bleeding from ischaemia (≈6%), ulcers (mainly jejunal, 5%), and perforation (5%). Acalculous ➔ cholecystitis can occur in ≈15%. ➔ Acute pancreatitis, ➔ appendicitis, and ➔ biliary strictures have all been reported.
- Acute hepatitis usually mild in patients with HBV-associated disease, although longer-term fibrosis can still develop. Segmental liver and splenic infarcts and ➔ Budd–Chiari syndrome have been reported secondary to respective vessel involvement.

Investigation

- ↑ ESR and CRP.
- Typically ANCA negative.
- Check HBV, HCV, and HIV serology.
- Patients with HBV-associated disease may develop secondary cryoglobuminaemia and hypocomplementaemia.
- Angiography: saccular or fusiform aneurysmal dilatations up to 1cm.
- Histology: segmental vascular inflammatory lesions, predominantly at branch points, with fibrinoid necrosis.

Treatment

Immunosuppression with high-dose → CORTICOSTEROIDS or cyclophosphamide usually required, with steroid-sparing agents in longer-term. Important to institute antivirals for HBV-associated disease.

Prognosis

French Vasculitis Group has developed Five Factor Score for prognosis. 5y survival >80%.

Polyposis syndromes

See: ➔ Colonic polyps and ➔ Hereditary polyposis.

Porphyrias

- Rate-limiting step in haem production is conversion of porphyrins (comprising four pyrrole rings) to δ-amino-laevulinic acid (ALA). In addition, haem provides negative feedback on δ-ALA synthase.
- Deficiency of specific enzymes (including δ-ALA synthase) leads to porphyrin accumulation. Porphyrias classified according to the site of porphyrin accumulation (Table 4.35) and pattern of symptoms: i.e. acute (neurovisceral) and cutaneous (photosensitive).[8]
- Acute intermittent porphyria and porphyria cutanea tarda are the most common porphyrias in GI practice.

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[8] Puy H *et al.* (2010). *Lancet* **375**: 924–37.

Table 4.35 Classification of porphyrias

Hepatic	Erythropoietic
Acute intermittent porphyria	X-linked sideroblastic anaemia
Porphyria cutanea tarda	Congenital erythropoietic porphyria
Hereditary coproporphyria	Erythropoietic protoporphyria
Variegate porphyria	

Acute intermittent porphyria (AIP)

Autosomal dominant. Incidence highest in Scandinavia (1/1,000). Symptoms triggered by alcohol, surgery, fasting, and any drug that induces CYP450. Occurs due to partial deficiency in porphobilinogen (PBG). Attacks rare before puberty or after menopause.

Clinical features

- Prodrome of behavioural change (e.g. anxiety, insomnia).
- Abdominal pain. Severe, usually lasts several days, and poorly localized, but no signs of peritonitis (see ▲ **Acute abdominal pain** ▲). Nausea and constipation. Physical examination often normal. Symptom free between episodes. Urine appears red-brown.
- Tachycardia, sweating, hypertension during acute episode.
- Polyneuropathy (motor-predominant peripheral neuropathy, mononeuritis multiplex, cranial nerve palsy), seizures, agitation, paranoia.

Diagnosis

Never made unless thought about (but, as with ➔ familial Mediterranean fever, immediate promotion for those who make the link in the patient with unexplained recurrent abdominal pain!).

- FBC: ↑ WCC during acute attack.
- U&Es: ↓ Na^+ may relate to syndrome of inappropriate ADH.
- AXR usually normal, or shows mild ileus.
- Urine tests:
    - Porphobilinogen (PBG) >4× ULN, ↑ δ-ALA, and uroporphyrin and coproporphyrin moderately ↑ during acute attack. Check laboratory routinely does PBG on screen (some don't!). PBG levels usually stay ↑ between attacks.
    - Little value in measuring urine porphyrins as can be ↑ in a number of other, more common, disorders.
    - Follow-up investigations if PBG positive will be under specialist guidance, but may include plasma spectroscopy, faecal porphyrins, and genotyping to refine diagnostic subtype.

Management

- Avoid drugs known to be contraindicated (check with 🖱 http://www.porphyriafoundation.com)
- High carbohydrate intake (oral, NG feed, or IV glucose infusion) inhibits haem synthesis. TPN rarely required.
- Opiate analgesia often required (see ➤ 'pain control', p. 135).

- Haemin infusion (e.g. Hematin 4mg/kg/d IV for 3–4d) in severe attack is effective, as provides negative feedback to haem synthesis, and so ↓ porphyrin production.
- 60–80% of patients never have another attack provided precipitants sought and avoided (e.g. check BNF before prescribing any drug).
- ➔ Liver transplantation considered if severe recurrent episodes.

Porphyria cutanea tarda (PCT)

- Most common type of porphyria. Occurs due to deficiency of hepatic uroporphyrinogen decarboxylase.
- Most cases sporadic (type I, 75%) or familial (type II, 25%), but also linked with other conditions (e.g. alcohol, ➔ hepatitis C, ➔ haemochromatosis).
- Presents with blistering skin rash or hyperpigmentation in sun-exposed areas (dorsum of hands, forearms, face).
- ↑ Plasma or urinary porphyrins.
- Dermatology opinion and skin biopsy may aid diagnosis.
- ↑ Iron levels (e.g. serum ferritin) may be found.
- Sun protection, phlebotomy, or desferrioxamine chelation for iron overload and chloroquine may be effective.

Portal hypertension

Background

- Defined as hepatic venous pressure gradient (HVPG; pressure between hepatic and portal venous systems) >5mmHg.
- Portosystemic collaterals (varices) develop when HVPG >12mmHg.
- Most commonly due to intrahepatic disease at site of liver sinusoid (e.g. cirrhosis), but pre- and post-sinusoidal causes also important (Table 4.36).
- ↑ Intrahepatic vascular resistance important because of fibrosis and disruption of microcirculation at sinusoid, but resistance may be dynamic, probably with role for myofibroblasts, derived from hepatic stellate cells. ↑ Portal blood flow also contributes.
- Bleeding due to varices occurs in 30–40% of patients with cirrhosis, with risk factors including variceal size and ➔ Child–Pugh score. Gastro-oesophageal region most common site for varices, but stomach, rectum, duodenum, and surgical anastomoses (e.g. stomas) can also be affected.

Clinical features

- Bleeding from gastro-oesophageal varices usually presents with haematemesis and melaena, with first bleeds carrying 25–50% mortality. Chronic blood loss and anaemia may occur due to portal hypertensive gastropathy (PHG).
- LUQ discomfort due to splenomegaly occasionally reported.
- Signs of chronic liver disease may be present, including ascites, splenomegaly, dilated superficial veins, and rectal haemorrhoids (see also ▸ Clinical examination of the gastrointestinal system, p. 131).

Table 4.36 Causes of portal hypertension

Pre-hepatic	Intrahepatic	Post-hepatic
➔ Portal vein thrombosis	*Pre-sinusoidal:* • Non-cirrhotic portal hypertension • ➔ Primary biliary cholangitis • ➔ Nodular regenerative hyperplasia • ➔ Sarcoidosis • ➔ Schistosomiasis • Congenital hepatic fibrosis	Inferior vena cava obstruction
Splenic vein thrombosis	*Sinusoidal:* • Cirrhosis • ➔ Alcoholic hepatitis	Cardiac disease (right heart failure, constrictive pericarditis)
Splanchnic arteriovenous fistula	*Post-sinusoidal:* • ➔ Budd–Chiari syndrome • ➔ Sinusoidal obstruction syndrome • ➔ Sarcoidosis	

Investigation

- Aimed at defining type of portal hypertension and underlying cause.
- Upper GI endoscopy showing varices confirms portal hypertension, and should be considered in all patients after diagnosing cirrhosis (see Table 4.37). Various grading systems used for variceal size used (broadly: small = grade 1, ≤25% lumen occluded on endoscopy; medium = grade 2, 25–50% lumen occluded; large = grade 3, ≥50% lumen occluded).
- Doppler US informs about abnormalities of hepatic and portal venous flow, portal vein thrombosis, and liver architecture. CT scanning with contrast and MRI also highly effective.
- Measurement of HPVG invasive and rarely necessary to make diagnosis, but allows clarification of whether cause is pre-sinusoidal, sinusoidal, or post-sinusoidal. Transjugular liver biopsy and portal venography can be performed at the same time.
- Other tests will depend on site of obstruction causing portal hypertension (e.g. see ➔ Budd–Chiari syndrome, ➔ schistosomiasis), and whether patient known to have liver disease (see ► Approach to well patients with abnormal liver tests). Liver function usually excellent in pre-sinusoidal portal hypertension. Portal hypertension *per se* may cause ↓ WCC and ↓ platelets due to hypersplenism.

Management

- Acute variceal bleeding is an emergency (see ▲ **Acute upper GI bleeding ▲**).
- Treat underlying cause of chronic liver disease (see ► Approach to cirrhosis and chronic liver disease).
- Prophylaxis—important, and often overlooked:
  - **Primary prophylaxis** (to prevent first bleed) indicated when moderate/large varices found on screening endoscopy (see Table 4.37). Non-selective β-blockers (e.g. propranolol 40–80mg PO bd or carvedilol 6.25mg PO od) lower portal pressure and ↓ risk of bleed (from 30% to 14% over 2y in patients with large varices), and most hepatologists use these as 1st-line therapy (but compliance may be poor and side effects preclude long-term use in 30%). Adjust dose to maintain heart rate at 60bpm. Variceal band ligation (VBL) equally effective (e.g. with 2–4-weekly endoscopies until eradicated), and should be used if side effects with β-blockers, but may precipitate bleeding in a few (e.g. post-banding ulcers) and of no benefit for gastric variceal/PHG bleeding.
  - **Secondary prophylaxis** (to prevent re-bleed) essential, as 60% of re-bleed in <1y. Combination of β-blockers and VBL more effective than either treatment alone. Early use of ➲ transjugular intrahepatic portosystemic shunt (TIPSS) after variceal bleed in cirrhotic patients at high risk of rebleeding improves long-term survival compared with standard secondary prevention.[9]
- Recurrent variceal bleeding that is difficult to control medically certainly an indication for ➲ TIPSS, and consideration of ➲ liver transplantation.

Controversy. Role of β-blockers in refractory ascites

While the beneficial role of non-selective β-blockers in cirrhotic patients is established, the effect in patients with refractory ascites is unclear. One study demonstrated ↑ incidence of paracentesis-induced circulatory dysfunction in patients that continued their β-blocker.[10] At present, no firm conclusions can be drawn. We recommend all patients on a β-blocker undergoing paracentesis be monitored closely for evidence of haemodynamic instability.

Table 4.37 Endoscopy and primary prophylaxis in compensated cirrhosis

Endoscopic finding	Action
No varices	Repeat endoscopy 2–3y
Small varices	Repeat endoscopy 1y
Medium-to-large varices	Lifelong β-blockers Variceal band ligation if intolerant of β-blockers

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[9] Afdahl NH & Curry MP (2010). *N Engl J Med* **362**: 2421–2.

[10] Sersté H *et al.* (2010). *Hepatology* **52**: 1017–22.

Portal vein thrombosis (PVT)

Background

Can occur in patients with or without cirrhosis. Cirrhotic PVT occurs in up to 25% of patients. Highest risk in patients with ➲ hepatocellular carcinoma. Thrombosis may involve only portal vein, or extend into splenic vein and splanchnic venous bed. Combination of local causes and systemic thrombotic predisposition important in development (Table 4.38).

Clinical features

- Acute PVT (usually defined as presentation within 2mo of thrombosis) may present with abdominal pain, fever, and signs of mesenteric infarction.
- Chronic PVT (also known as portal cavernoma) presents with complications of ➲ portal hypertension. Splenomegaly and hypersplenism common, but ascites rare (unless associated liver disease). Variceal bleeding occurs in 30%, but excellent prognosis due to preserved liver function (may also explain low rate of ▲ **hepatic encephalopathy** ▲. 10y survival >80% in absence of cirrhosis.
- Biliary abnormalities (due to compression by varices or variceal mass around portal vein—'cavernoma') seen in 80%, but obstructive jaundice due to ➲ biliary stricture rare.

Investigation

Aimed at defining cause (can be found in 80%) and thrombus extent:

- PVT accurately diagnosed with Doppler US, contrast CT, EUS, and MRI. Formal angiography rarely required.
- Bloods may show signs of hypersplenism (↓ WCC, ↓ platelets).
- Tests for prothrombotic tendency essential if no clear cause identified (Table 4.39).

Table 4.38 Causes of portal vein thrombosis

➲ Cirrhosis	Post-surgical (e.g. ➲ liver transplantation)
➲ Portal hypertension (any cause)	Umbilical vein catheterization
Prothrombotic tendency	PV compression by nodes (e.g. ➲ TB, ➲ lymphoma)
Malignancy (local/distant)	Drugs (e.g. ➲ oral contraceptive pill, didanosine)
Sepsis (local/systemic)	Pregnancy/post-partum
➲ Schistosomiasis	➲ Pancreatitis (➲ Acute and ➲ Chronic pancreatitis)

Table 4.39 Prothrombotic factors associated with portal vein thrombosis

Myeloproliferative disorders, including polycythaemia rubra vera (check for *JAK2* mutation), essential thrombocytosis, myelofibrosis	G20210A prothrombin gene mutation
Antiphospholipid syndrome (check for cardiolipin antibody)	Hyperhomocysteinaemia
➔ Behçet's disease	Factor V Leiden deficiency
Protein C, S (may be falsely ↓ in chronic liver disease), or antithrombin III deficiency	Paroxysmal nocturnal haemoglobinuria

Management

- No randomized trials to guide management.
- See ▲ **acute upper GI bleeding** ▲ for management of variceal bleeding.
- Small studies suggest resolution of acute PVT in 80% of cases with prompt anticoagulation (heparin followed by warfarin). Duration of anticoagulation uncertain: minimum 3mo, but may need lifelong if thrombotic tendency persists (as for pulmonary emboli).
- In chronic PVT, no clear consensus on variceal bleeding prophylaxis as RCTs performed in patients with chronic liver disease and the rate and severity of bleeding in isolated PVT is low, but secondary prophylaxis probably indicated (see ➔ portal hypertension). Recent large case series suggest oral anticoagulation does not lead to ↑ frequency or severity of variceal bleeding, and may ↓ mortality due to mesenteric infarction. Pragmatic approach may be consideration of warfarinization after eradication of gastro-oesophageal varices with endoscopic band ligation.
- Surgical portosystemic shunt and ➔ TIPSS considered for recurrent bleeding. Low rate of ▲ **hepatic encephalopathy** ▲.
- Interval imaging (CT/MRI) required to assess for extension, resolution, or recanalization.

Portopulmonary hypertension

Characterized by pulmonary arterial hypertension and portal hypertension, with or without advanced liver disease. Prevalence 5–9% in patients undergoing ➔ liver transplant assessment. Risk factors include ➔ autoimmune hepatitis and ♀ gender. Pathogenesis unclear but proposed mechanisms include pulmonary vasoconstriction secondary to vasoactive mediators.

Clinical features

- Progressive dyspnoea, syncope, orthopnoea.
- Accentuated pulmonary component of 2nd heart sound.
- Peripheral oedema.

Diagnosis

- Exclude other causes of pulmonary hypertension.
- ECG: right axis deviation, right bundle branch block.
- Transthoracic echocardiogram.
- Lung function tests: ↓ lung volumes and forced vital capacity.
- Right heart catheterization: mean pulmonary artery pressure >25mmHg, pulmonary capillary wedge pressure <15mmHg.

Treatment

- Poor prognosis without treatment.
- Treatment of pulmonary hypertension with vasomodulators (e.g. sildenafil, bosentan, epoprostenol).
- Response assessed with serial echocardiograms and exercise tolerance using 6-minute walk test.
- ➲ Liver transplantation option for patients with mean pulmonary arterial pressure <50mmHg.

Post-gastrectomy syndromes

Gastrectomy and acid reduction surgery (vagotomy) rates have ↓ dramatically over recent decades owing to advent of → PROTON PUMP INHIBITORS, treatment of ➲ *H. pylori*, advances in endoscopic techniques, and changes in surgical approach. Vagotomy (sometimes performed with pyloroplasty to disrupt pyloric sphincter), gastric resection or bypass procedures cause permanent anatomical and physiological changes resulting in:

- ↓ Reservoir function.
- Altered gastric adaptation.
- Altered gastric emptying.
- Duodenal reflux into stomach.
- Altered absorptive capacity.

Early complications

- Early delayed gastric emptying follows widespread denervation of stomach.
- Pain and distension 30–60min after meals as a result of rapid emptying of stomach and jejunal distension. Usually settles as patient learns new eating habits.

Delayed gastric emptying

- Chronic gastroparesis can occur following truncal vagotomy, and can be difficult to treat. Metoclopramide and erythromycin may help, but sometimes further surgery with Roux-en-Y anastomosis needed to return patient to oral feeding.
- Anastomotic ulcers can occur due to ↓ resistance to acid digestion of jejunum, gastric stasis, and partial obstruction of anastomosis due to scarring or oedema. Biopsy of ulcer to exclude malignancy may be needed and revisional surgery often required.
- ➲ Afferent loop syndrome.

- Reflux of duodenal contents (bile and pancreatic secretions) into gastric remnant can cause pain and vomiting. Endoscopic biopsy may show features of a chemical gastritis. Response to PPI and prokinetics often poor and, in severe cases, operative treatment necessary (conversion to Billroth I or Roux-en-Y configuration)
- There is a twofold risk of gastric cancer 15y after gastrectomy, probably due to reflux-stimulated increases in cell proliferation.

Rapid emptying

Post-vagotomy diarrhoea is poorly understood, but patients usually have rapid gastric emptying. Codeine and loperamide can help, as can → OCTREOTIDE. ➲ Dumping discussed elsewhere.

Metabolic complications

- Iron-deficiency anaemia. Common. Apart from recurrent ulceration, ↓ gastric acid impairs absorption of ferric iron. Can take several months to develop due to moderately large bone marrow stores.
- Intrinsic factor absent after total gastrectomy, which can lead to B_{12} deficiency. May take several years to develop due to large amounts of B_{12} stored in liver.
- Steatorrhoea can result from poor mixing of food with pancreatic enzymes or ➲ afferent loop syndrome.
- Calcium deficiency with ➲ osteoporosis and ➲ metabolic bone disease can result from rapid transit through upper GI tract and ↓ absorption due calcium binding tightly to unabsorbed dietary fat, impairing its absorption.

Pouchitis

Inflammation occurring in an ileal pouch after proctocolectomy with ⊳ ileal pouch–anal anastomosis or ⊳ Koch's continent ileostomy. Risk highest in 1st 12mo after ileostomy, ranging from 20 to 35%. After 10y, 50% of patients will have had at least 1 episode. Acute episodes (<4wk duration) do not affect long-term pouch function, but chronic pouchitis (affecting 10%) is associated with dysplasia and carcinoma, probably via dysplasia in rectal cuff. Risk factors include ➲ ulcerative colitis, smoking (↑ acute but ↓ chronic pouchitis), NSAID use, or multiple previous abdominal or pelvic surgeries.

Aetiology

Unknown, but probably relates to anaerobic colonization of pouch mucosa and subsequent colonic metaplasia. Patients with IBD (especially those with extraintestinal manifestations) more commonly affected than those with ➲ familial adenomatous polyposis. Exclusion of other superimposed infections is a concern, as is the possibility that patient had ➲ Crohn's disease all along.

Clinical features

Diarrhoea, bleeding, urgency, abdominal pain. Accurate diagnosis requires combination of endoscopic, clinical, and histological assessments. Reliance on clinical assessment alone results in overdiagnosis and unnecessary treatment. Scoring systems have been developed to standardize evaluation and response to treatment; best is the PDAI (Table 4.40). Pouchitis defined as score >7. Endoscopic pouch surveillance required to exclude neoplasia in patients with underlying IBD.

Table 4.40 Pouchitis Disease Activity Index (PDAI)

Criteria	Score
Clinical	
Stool frequency (usual; 1–2 more than usual; 3+ more than usual)	0–2
Rectal bleeding (none/rare; present daily)	0–1
Faecal urgency/cramps (none; occasional; usual)	0–2
Fever	1 if present
Endoscopic	
Oedema, granularity, friability, loss of vascular pattern, mucous exudates, ulceration	1 for each if present
Histological	
Polymorph infiltration: mild, moderate, severe	1–3
Average ulceration per low power field: <25%; 25–50%; >50%	1–3

Treatment

- **Primary prophylaxis** VSL#3® (oral probiotic) ↓ incidence compared with placebo.
- Acute pouchitis:
  - Simple antidiarrhoeal agents may help.
  - Antibiotics 1st line for true pouchitis (metronidazole 400mg PO tds or ciprofloxacin 500mg PO bd for 5–7d; combination of both may have ↑ efficacy).
  - Topical → 5-AMINOSALICYLATE or steroid enemas can help.
  - Patients with antibiotic-dependent pouchitis should be trialled on maintenance VSL#3® therapy or low dose antibiotics (ciprofloxacin or rifaximin).
- **Chronic pouchitis:**
  - Avoid NSAIDs.
  - Investigate other causes (infection, ischaemia).
  - Initiate oral or topical → 5-AMINOSALICYLATE.
  - Topical hydrocortisone or budesonide can be trialled in those not responding. Further escalation to → AZATHIOPRINE or → ANTI-TNF can be considered in patients who fail to improve after 8wk of budesonide.

Pregnancy

See: ▶ Approach to GI problems in pregnancy and ▶ Approach to liver problems in pregnancy.

Primary biliary cholangitis (PBC)

Epidemiology and pathogenesis

Previously known as primary biliary 'cirrhosis', but name changed to 'cholangitis', partly to reflect pathology but also due to stigmatization as perception that the general public associate 'cirrhosis' with 'alcohol misuse'. Chronic progressive cholestatic disorder, predominantly of middle-aged ♀ (90%). Prevalence: 20–400/ million. Aetiology unclear, but environmental trigger (e.g. bacteria, viruses) in genetically susceptible individuals (familial link shown) suggested.

Clinical features

- Pruritus and fatigue are classic presenting features, but 50% identified in asymptomatic stage. Associated with other autoimmune diseases: sicca syndrome (80%), thyroid disease, Raynaud's disease, arthralgia, Addison's disease. ➲ Osteoporosis common. Increased risk of ➲ hepatocellular carcinoma (although lower than for chronic viral ➲ hepatitis, ➲ haemochromatosis, and ➲ alcoholic liver disease).
- Clinical signs include xanthelasma around eyes, excoriations due to pruritus, clubbing, and signs of chronic liver disease.
- Median survival from presentation 10–16y for asymptomatic, and 7–10y for symptomatic, patients.

Investigations

- ↑ ALP, ↑ γGT, with transaminases raised only mildly. ↑ Bn occurs late, and then usually inexorable.
- ↑ PT may be due to impaired synthetic function or E vitamin K malabsorption.
- ↑ Serum IgM.
- Antimitochondrial antibodies (AMA) ≥1:40 in 95%. AMA against M2 antigen highly specific. If negative, but histological features of PBC and ↑ ANA titres, it is probably 'autoimmune cholangitis', a variant of PBC (see ➲ overlap syndromes).
- US performed in all cases to exclude biliary obstruction (see ▶ Approach to well patients with abnormal liver tests).
- ➲ Liver biopsy not mandatory where diagnosis clear, but allows inflammatory activity and fibrotic stage to be assessed. Four histological stages (although lesion distribution may be patchy):
  - I: Florid bile duct lesions, portal hepatitis, granulomas.
  - II: Periportal fibrosis and hepatitis, portal tract enlargement, ductular proliferation.
  - III: Bridging necrosis, septal fibrosis, scarring.
  - IV: Cirrhosis.
- DEXA scan (see ▷ 'bone densitometry', p. 167), calcium, and parathyroid hormone levels to investigate bone disease.
- Measure fat-soluble vitamins (➲ vitamins A, ➲ D, ➲ E, ➲ K).

Management

- Complications of cirrhosis managed along standard lines (see ► Approach to cirrhosis and chronic liver disease).
- → URSODEOXYCHOLIC ACID (UDCA) 10–15mg/kg/d safe, well tolerated, and ↓ likelihood of transplantation and death. Best responses seen in stage I and II disease, and if >40% improvement or normalization of ALP seen after 1y of treatment ('Barcelona criteria').
- → OBETOCHOLIC acid (OCA) 5–10mg od now licensed as 2nd line therapy.
- Fibrates (e.g. bezafibrate) may be an alternative to OCA. Renal function monitoring is recommended.
- Management of suboptimal responses to above not established, but for pruritus give → COLESTYRAMINE 4g PO qds. Alternatives include rifampicin 150mg PO od, naltrexone 25–50mg PO od (then titrate up if needed), or sertraline 50mg PO od.
- Fatigue difficult to manage, but worth excluding other causes such as hypothyroidism and anaemia.
- Treat ➲ osteoporosis and osteopaenia if present. Low threshold for calcium/vitamin D supplements (e.g. Calcichew® D3 Forte 1 tablet bd), even without DEXA scan.
- If vitamin deficient, give oral vitamin A 10,000IU/d, vitamin D + calcium (as mentioned), vitamin E 400IU/d ± vitamin K 5–10mg/d.
- ➲ Liver transplantation highly effective (> 80% 5y survival), and may be indicated for intractable pruritus, as well as progressive liver failure (MELD score >12), and serum Bn >100μmol/L.

Primary sclerosing cholangitis (PSC) (see Plate 40)

Epidemiology and pathogenesis

Chronic cholestatic liver disease characterized by biliary stricturing and dilatation. Prevalence: 6/100,000. Associated with ➲ inflammatory bowel disease in 80% of cases (>80% will have ➲ ulcerative colitis), although only 3–10% of patients with IBD develop PSC.

Immunogenetic factors (e.g. association with HLA A1, B8, DR3) and environmental factors (e.g. portal venous endotoxins/bacteria) likely to be important, but exact aetiology unclear.

Clinical features

Presents with fatigue, pruritus, jaundice, and RUQ discomfort.

- Jaundice may result from intrahepatic stricturing, impaired liver function, 'dominant' extrahepatic biliary stricture (20%), biliary stone disease, or ➲ cholangiocarcinoma (lifetime risk 20–30%).
- Features of cholangitis (fever, pain, jaundice) usually occur following instrumentation (e.g. ERCP), rather than *de novo*.
- Signs of chronic liver disease and ➲ portal hypertension may be present.

- ➲ Osteoporosis, ➲ metabolic bone disease, and steatorrhoea may occur.
- Time from symptomatic presentation to death or ➲ liver transplant 12–21y.
- 'Small duct PSC' displays biochemical, clinical, and histological features of PSC, but with normal biliary imaging. Carries better prognosis than large duct PSC, with lower/no ➲ cholangiocarcinoma risk.

Investigation

- LFTs show cholestatic pattern (↑ ALP, γGT), but with AST/ALT <5× ULN. Bn often fluctuates (unlike in ➲ primary biliary choangitis), with ↑ related to cholangitis, biliary stones, and strictures.
- MRCP can demonstrate cholangiographic changes of multifocal intrahepatic and extrahepatic stricturing and beading, and avoids risks of ERCP. See Box 4.65 for differential diagnosis.
- Liver biopsy often not diagnostic, but histological features include bile duct proliferation, ductopaenia, and concentric peribiliary fibrosis ('onion skin').
- p-ANCA ↑ in 65–85%.
- Serum IgG4 ↑ in 6–12%. May represent overlap with IgG4-sclerosing cholangitis (see also ➲ autoimmune pancreatitis). Importantly, ↑ IgG4 in PSC strongly predicts more rapid progression to liver failure and transplantation.
- Diagnosis of ➲ cholangiocarcinoma in PSC always difficult at early stage, but combination of CT, biliary brush cytology at ERCP, and serum tumour markers ➤ CEA and ➤ CA19–9 used (although CA19–9 >180U/ml reported to be >95% specific and >66% sensitive, high levels are also seen in biliary obstruction).
- Colonoscopy should be performed in all patients with new diagnosis of PSC (80% have histological evidence of colitis, often subclinical). In PSC, colitis more commonly pancolitis with rectal sparing and backwash ileitis. If colitis found, annual surveillance colonoscopy recommended in view of markedly ↑ ➲ colonic cancer risk.
- Annual abdominal US should be considered, because of risk of malignant ➲ gallbladder polyps/➲ gallbladder cancer.

Box 4.65 Differential diagnosis of PSC

- Biliary stone disease.
- Post-cholecystectomy ➲ biliary strictures.
- ➲ Caroli's disease.
- Infective (TB, HIV cholangiopathy, ➲ *Clonorchis*.
- ➲ Cholangiocarcinoma.
- Portal hypertensive biliopathy.
- Ischaemic strictures.
- Exposure to biliary toxins (e.g. formalin).
- IgG4-sclerosing cholangitis.

Management

- Role of → URSODEOXYCHOLIC ACID (UCDA) remains controversial. Improvements in LFTs, but no effect on symptoms, histology, or survival, shown with UDCA 13–15mg/kg/d. Against expectations, a large placebo-controlled trial showed ↑ mortality with UDCA 28–30mg/kg/d compared with placebo.[11] Most hepatologists give UDCA 15–20mg/kg/d, which has not been shown to carry adverse outcome; benefit for liver uncertain, but ↑ evidence for chemoprevention of colorectal cancer in PSC patients with colitis.
- Steroid therapy has no general role but may provide benefit in subset of patients with ↑ IgG4. This is being further studied.
- 'Dominant' extrahepatic biliary strictures should be managed endoscopically, with balloon dilatation. Vital to exclude ➔ cholangiocarcinoma (with biliary brushings and endobiliary biopsies ± cholangioscopy) at time of ERCP.
- → ANTIBIOTICS (e.g. → CIPROFLOXACIN) given as prophylaxis prior to ERCP for PSC, given risk of incomplete biliary drainage.
- Pruritus managed initially with → COLESTYRAMINE 4g/d. Rifampicin 150mg PO OD or naltrexone 25–50mg PO od (titrated up if needed) can also be used.
- Correct ➔ vitamin A, ➔ D, ➔ E, and ➔ K deficiencies, if present.
- ➔ Liver transplantation provides 80–90% 5y survival, but 20% 5y recurrence. ➔ Cholangiocarcinoma is an absolute contraindication in most centres.

Prokinetics

See: → PROKINETICS.

Protein-losing enteropathy

Excess protein loss from gut (which is non-selective and not limited to low molecular weight proteins, as in nephrotic syndrome). Normal daily enteric protein loss ~1–2% of serum pool; can ↑ to up to 60% in protein-losing enteropathies. Causes (see also Box 4.66):[12]

- Mucosal ulceration.
- ↑ Mucosal permeability.
- Lymphatic obstruction.

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[11] Chapman R *et al.* (2010). *Hepatology* **51**: 660–78.

[12] Umar SB & DiBaise JK (2010). *Am J Gastroenterol* **105**: 43–9.

Box 4.66 Causes of protein-losing enteropathy

Erosive GI disease
- ➔ Inflammatory bowel disease.
- GI malignancy, including ➔ lymphoma.
- ➔ NSAID enteropathy.
- ➔ Graft-versus-host disease.
- ➔ Sarcoidosis.

Non-erosive GI disease
- ➔ Coeliac disease.
- Hypertrophic gastropathy (e.g. ➔ Ménétrier's disease).
- ➔ Eosinophilic gastroenteritis, lymphocytic gastroenteritis.
- Connective tissue diseases.
- Small bowel ➔ bacterial overgrowth.
- ➔ Amyloidosis.
- ➔ Whipple's disease.
- ➔ Tropical sprue.

Increased interstitial pressure
- Intestinal ➔ lymphangiectasia or lymphatic malformation.
- Congestive cardiac failure.
- Fontan procedure for single cardiac ventricle.
- Portal hypertensive gastropathy.
- ➔ Mesenteric venous thrombosis.
- Sclerosing mesenteritis.

Clinical features

- Oedema (including ascites, and pleural/pericardial effusions), fat or carbohydrate malabsorption, fat-soluble ➔ vitamin deficiency, and consequences of ↓ humoral immunity. Some patients experience diarrhoea, although overall GI symptoms are uncommon.
- Laboratory abnormalities may include ↓ serum albumin, Igs, proteins (e.g. caeruloplasmin, α_1-antitrypsin, transferrin, hormone binding proteins), and lymphopaenia if lymphatic obstruction.

Diagnosis

- Need to exclude malnutrition, liver, and renal disease.
- Gold standard is measuring loss of IV-labelled albumin, but disadvantages in terms of radioactive exposure and expense.
- α_1-antitrypsin (A1AT) clearance into faeces is test that best counterbalances accuracy with pragmatic considerations:
  - Requires paired blood sample and 24h stool sample. Normally ≤27ml/24h (or ≤56ml/24h in patients with diarrhoea).
  - Random faecal A1AT measurement is not reliable substitute.
  - Perform test while patient receiving acid suppression therapy as A1AT degraded at pH <3.
  - Cannot be used to measure gastric protein loss, and interpretation difficult in patients with positive ➢ faecal occult blood.
- May require imaging for lymphatic abnormalities, or endoscopy with biopsy for diagnosis of GI mucosal disorders.

Management

- Largely directed at underlying cause, alongside correction of nutritional deficiencies. High protein diet advised (may need 2–3g/kg/d).
- → OCTREOTIDE may ↓ fluid secretion and protein exudation.
- Intermittent albumin infusions generally unhelpful in long-term.
- Support stockings may be helpful for lower limb oedema, but keep close eye on skin integrity. Diuretics typically not useful as oedema secondary to ↓ oncotic pressure rather than Na^+/water overload.
- Surgery reserved for refractory inflammatory causes.

Proton pump inhibitors

See: → PROTON PUMP INHIBITORS.

Protozoa

See: ➔ Amoebiasis, ➔ Giardiasis, ➔ Coccidia, ➔ Microsporidia, and ➔ Trypanosomiasis.

Pruritus ani

Perianal area is the most common site for intractable itching, due to:

- Benign anorectal condition such as ➔ haemorrhoids or anal fissure.
- Neoplasia (Bowen's disease, Paget's disease, ➔ anal cancer).
- Dermatological disease (dermatitis, lichen sclerosis).
- Infection: *Candida*, threadworm (more common with underlying systemic disease such as diabetes).
- Possible dietary components: coffee implicated as common irritant.
- Before labelling condition as 'idiopathic', consider faecal leakage: ➢ anorectal manometry and endoanal US will help to define defect in anal sphincters.

Treatment involves identifying cause. Advice sheet may help (Box 4.67): single most important component is to avoid vigorous wiping or 'polishing'.

Box 4.67 Advice sheet for pruritus ani

- Avoid creams and ointments if possible. Short-term steroids (1% hydrocortisone ointment) can help. Long-term use thins skin.
- Wash skin with water after each stool. Pat dry; do not rub.
- Wear cotton underclothing and stockings rather than tights.
- Avoid hot and spicy foods that cause wind and loose stools.
- Wear cotton pad or folded sheet of toilet paper to absorb any mucus or moisture seeping from the anus.
- Avoid scratching at all times.

Pseudo-achalasia

Appearance usually seen on barium swallow or endoscopy that can mimic ➔ achalasia, but in fact due to malignant compression of lower oesophagus. Accounts for ≈5% of cases of manometrically defined achalasia, and should be suspected in over-50 age group if onset of symptoms abrupt (<1y) or early weight loss >7kg. Should also be considered if feeling at endoscopy of resistance or stiffness in crossing lower oesophageal sphincter, or if patient tolerates endoscopic dilatation very poorly (in this case, stop procedure and reconsider diagnosis). Adenocarcinoma of gastro-oesophageal junction is the most common cause, but other tumours and infiltrative diseases have been reported (see ➔ oesophageal tumours).

Pseudo-membranous colitis

See: ➔ Clostridial infections of GI tract.

Pseudomonas

- Can colonize every portion of GI tract. Most commonly affects very young children and adults with haematological malignancies and chemotherapy-induced neutropaenia (in whom gut is an important portal of entry for pseudomonal bacteraemia). Spectrum of disease ranges from very mild symptoms to severe necrotizing enterocolitis with significant morbidity and mortality.
- Epidemics of pseudomonal diarrhoea occur in nurseries. Infants present with irritability, vomiting, diarrhoea, and dehydration.
- Infection can cause enteritis, and in its most severe form can present with prostration, headache, fever, and diarrhoea (‘Shanghai fever’).
- *Pseudomonas typhlitis* typically presents in patients with neutropaenia resulting from acute leukaemia, with sudden onset of fever, abdominal distension, and worsening abdominal pain.
- Treatment generally requires extended spectrum antibiotics. Liaise with microbiology regarding local choice of recommended agent(s).

Pseudo-obstruction

Symptoms and signs of intestinal obstruction in absence of occluding lesion. Caused by disorders of smooth muscle, myenteric plexus or extraintestinal nervous system (see Box 4.68). ➔ Ogilvie’s syndrome is acute pseudo-obstruction localized to the colon, precipitated by trauma, orthopaedic surgery, obstetric procedures, pelvic surgery, or electrolyte disturbances (e.g. $\downarrow K^+$, $\downarrow Mg^{2+}$).

Box 4.68 Causes of chronic intestinal pseudo-obstruction

- Disorders of smooth muscle:
- Primary. Due to rare visceral myopathies.
- Secondary: ➲ amyloidosis, ➲ radiation, ➲ SLE, ➲ systemic sclerosis).
- Disorders of myenteric plexus.
- Neurological problems: ➲ Parkinson's disease, dysautonomia.
- Small bowel diverticulosis.
- Endocrine: hypothyroidism, ➲ porphyria.
- Drugs (→ OPIATES, phenothiazines, → ANTICHOLINERGICS, tricyclics, calcium channel blockers).

Clinical features

Varying degrees of abdominal pain, distension, and vomiting, depending on which part of the bowel is involved. Small bowel involvement with stasis and ➲ bacterial overgrowth may cause steatorrhoea (resulting in weight loss and malabsorption). May be gastroparesis (with succession splash) or oesophageal involvement.

Investigations

- Air-fluid level may be seen on AXR.
- Blood tests directed to diagnoses listed Box 4.68.
- CT/MRI ± endoscopy to exclude mechanical obstruction.
- May require brain MRI, electromyography, nerve conduction studies, autonomic function tests, and/or gut transit studies, depending on likely/possible cause.
- Association with urinary tract involvement such as megacystis or megaureters.

Treatment

- Normalise electrolytes, especially potassium, calcium, and magnesium.
- Drug treatment with → PROKINETICS attractive but → METOCLOPRAMIDE and → DOMPERIDONE rarely work.
  - Cisapride more effective but restricted to named-patient basis.
  - Erythromycin is a motilin agonist and sometimes tried.
  - → OCTREOTIDE in small doses can induce migrating motor complexes in small intestine.
  - Broad-spectrum antibiotics useful for ➲ bacterial overgrowth due to stagnant loop syndrome.
- Diet should be low fat, low residue, and low lactose. Nutritional support may be required if patients have ↓ food intake. Small number of patients need home ➲ parenteral nutrition.
- Colonoscopic decompression can be tried although not universally effective.
- Neostigmine 2.5mg IV over 2–3min (patient should be on cardiac monitor with atropine ready in case of bradycardia) effective in prospective controlled study,[13] and probably underutilized.

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[13] Ponec RJ *et al.* (1999). *N Engl J Med* **341**: 137–41.

- Prucalopride 2mg PO od (1mg if age >65y) is a $5HT_4$ receptor agonist. Accelerates transit through stomach, small and large bowel.
- Surgery rarely required and does not always remove symptoms. Also case reports of colonoscopic insertion of gastrostomy tube into colon successfully relieving obstructive symptoms.

Pyloric stenosis

Usually associated in adults with ➔ peptic ulcer disease or ➔ gastric cancer. Hypertrophic pyloric stenosis is rare.

Clinical features

Nausea, vomiting, early satiety, and epigastric pain after eating. Unlike in infants, physical examination often not helpful because in adults pyloric mass is difficult to palpate. Succussion splash may sometimes be elicited. Identical symptoms and signs found in gastric outlet obstruction due to duodenal stricturing in ➔ pancreatic cancer.

Diagnosis

- Can be via barium radiology, although US or CT more effective at revealing extraluminal pathology that may be causing stenosis.
- Endoscopy needed to diagnose peptic ulceration or tumour, and to make histological diagnosis.

Treatment

If malignancy excluded, endoscopic balloon dilatation can be effective, although post-procedure recurrence ~80%. Placement of jejunostomy tube should be considered as patients usually significantly malnourished. Surgical pyloromyotomy or resection of involved region can offer long-term cure. Gastric bypass may be necessary.

Pyoderma gangrenosum

Neutrophilic dermatosis. Cutaneous papule or pustule that rapidly evolves into large, painful necrotic ulcer with violaceous border (Plate 45).[14] Most often seen on leg but sometimes occurs around stoma. Incidence: 3–10/million. Demonstrates pathergy (development of ulcers in response to minor trauma; shared with skin lesions of ➔ Behçet's disease) in 20–30%. Associated with systemic disease in 50%, particularly ➔ ulcerative colitis and ➔ Crohn's disease.[15] Variable correlation with intestinal disease activity, and peri-stomal disease usually arises months to years following surgery. Responds to high-dose → CORTICOSTEROID, immunosuppressants (particularly → CICLOSPORIN), and → ANTI-TNF. Heals with cribriform scarring if diagnosis delayed, which can be disfiguring.

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[14] Teagle A & Hargest R (2014). *J Roy Soc Med* **107**: 228–36.

[15] Agarwal A & Andrews JM (2013). *Aliment Pharmacol Ther* **38**: 563–72.

Section 4

R

Radiation damage to the GI tract *530*
Reactive arthritis *531*
Rectal cancer *532*
Rectal prolapse *533*
Rectal ulcer: see ➔ Solitary rectal ulcer syndrome *534*
Rectocoele *534*
Refeeding syndrome *534*
Reiter's syndrome: see ➔ Reactive arthritis *536*
Retroperitoneal haemorrhage *536*
Retroperitoneal perforation *537*
Rheumatoid arthritis and the GI tract *537*
Rockall score: see ➔ Scoring systems for predicting outcomes in GI bleeds *538*
Rotavirus *538*
Rotor syndrome *538*
Roundworm (nematode) infection *538*

Radiation damage to the GI tract

Bowel can be damaged by radiation treatment for a range of tumours (including cervical or prostate cancer), or combined chemoradiotherapy for ➔ rectal cancer. Effects of radiation on tissue depend on:

- Rate of cell division (cell turnover is higher in the small intestine, which is therefore more sensitive to radiation damage).
- Presence of genes regulating apoptosis. Experimentally, radiation-induced apoptosis depends on the presence of p53 and is inhibited by bcl2; higher levels of bcl2 in the colon and rectum may explain the greater tolerance to radiation compared with small intestine.
- Ionizing radiation activates inflammatory and fibrogenic cytokines. TGF-β promotes fibrosis by stimulating fibroblast chemotaxis and collagen synthesis.

Risk factors

- Dose and duration of radiotherapy.
- Combination of radiotherapy with chemotherapy.
- ↓ Bowel motility.
- Vascular disease (e.g. patients with diabetes or atherosclerosis, or collagen vascular disease such as rheumatoid arthritis or SLE).
- ➔ Inflammatory bowel disease.

Epidemiology

- Acute radiation enteritis is common (incidence 20–70%), usually occurs in 3rd week of fractionated course, and rarely life-threatening unless also develop pancytopaenia and sepsis secondary to chemotherapy. Usually resolves 2–6wk after completion of radiotherapy.
- Chronic radiation enteritis varies in incidence from 1 to 15%. Latency may range from 6mo to 25y. Predisposing factors include older age, postoperative radiation, collagen vascular disease, combined chemotherapy, and poor radiation technique. Prolapse of small bowel into pelvis after surgery exposes large volumes of bowel to radiation.

Pathology

Occlusive vasculitis and diffuse collagen deposition with fibrosis. Changes are progressive and result in mucosal ulceration, necrosis, and sometimes perforation.

Clinical features (see Plate 26)

- Acutely, patients may present with diarrhoea, abdominal pain, nausea, or vomiting.
- Symptoms of acute/subacute small bowel obstruction (post-prandial pain, bloating, vomiting, constipation) due to chronic strictures.
- Fistulae and abscesses.
- ➔ Bacterial overgrowth may be due to dilated bowel loops proximal to stricture.
- Patients with history of pelvic irradiation can present with rectal bleeding due to mucosal friability or telangiectasia. May have anorectal pain, tenesmus, or faecal urgency. Chronic inflammation can lead to ↓ rectal capacity and diarrhoea.

Diagnosis

- Not always straightforward. Analysis of treatment plan and dose distribution may show areas of high dose, and lesions found on imaging or endoscopy usually localized to these areas.
- Recurrence of cancer often needs excluding because manifestations of chronic radiation colitis are non-specific. Mucosal ulceration and thickening of small bowel loops are radiological signs of radiation damage. Imaging requires adequate luminal distension: ▷ CT enteroclysis with infusion of contrast through nasoenteric tube probably best single investigation, with good sensitivity and specificity for diagnosing recurrent tumour and low-grade or intermittent obstruction. Can also help in suggesting source of occult bleeding.
- Colonoscopy helpful if rectal bleeding, can help diagnose cause of stricturing, and look for recurrent or further new primary tumours.

Management

- Be as conservative as possible – prevention is the best treatment. Surgery difficult and associated with high morbidity. Management of pelvic fistulae complex and requires diversion before corrective surgery.
- Avoid high-fibre diet (e.g. fruits, vegetables, whole grains).
- Diarrhoea can result from fast transit time, ➲ bile acid malabsorption, and ➲ lactose intolerance. Loperamide can ameliorate.
- Antibiotics can help if ➲ bacterial overgrowth.
- ▷ Laser therapy or ▷ argon plasma coagulation (APC) can control rectal bleeding due to radiation proctitis, and recent reports suggest → SUCRALFATE enemas or local formalin treatment (given under general anaesthetic) may be of value.
- Hyperbaric oxygen stimulates new blood vessel formation, but clinical outcomes of observational studies are conflicting. Small bowel transplantation might offer hope to small number of paediatric patients with radiation enteritis.
- Pharmacological agents conferring protection against effects of ionizing radiation (e.g. amifostine) attractive but unproven.

Reactive arthritis

Autoimmune disorder occurring 1–4wk after triggering GI or urogenital tract infection. Complicates 1–2% of cases of ➲ *Shigella*; also reported following ➲ *Salmonella*, ➲ *Yersinia*, and ➲ *Campylobacter*. Often occurs as triad of large joint inflammatory arthritis, conjunctivitis/uveitis, and urethritis. Previously known as Reiter's syndrome, but eponym fallen out of favour as Reiter was not the first to describe and also convicted of Nazi war crimes. Patients may develop psoriasiform skin lesions, including keratoderma blennorrhagica (Plate 49) and circinate balanitis, and Achilles tendon enthesitis. Most common in ♂ age 20–40y who are HLA-B27 positive (Box 4.69). Stool cultures and screening for sexual transmitted infections may support diagnosis, but often negative by time arthritis emerges.[1] Antibiotic therapy typically not indicated as enteric infection resolved by presentation. Arthritis can be chronic and relapsing. Treatment symptomatic ± NSAIDs.

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[1] Selmi C & Gershwin ME (2014). *Autoimmun Rev* **13**: 546–9.

Box 4.69 HLA-B27 and enteric arthropathy

- ➔ Reactive arthritis: 80% positive for HLA-B27. Conversely ~20% of HLA-B27 patients develop reactive arthritis after bacillary dysentery.
- Ankylosing spondylitis and ➔ ulcerative colitis/➔ Crohn's disease.
- Sacroiliitis complicating ➔ Whipple's disease.
- ➔ Behçet's disease.

Rectal cancer

Epidemiology and pathogenesis

Accounts for 30% of colorectal cancer. Epidemiology, aetiology, pathogenesis, and screening recommendations common to ➔ colon cancer.

Evaluation and staging

- Digital rectal examination and endoscopy with biopsy are important.
- Consider colonoscopy in all, to exclude additional proximal lesions which may change management.
- Preoperative staging essential to determine most appropriate management, including whether candidate for preoperative therapy and most appropriate surgical option (radical resection vs. local excision).
- MRI pelvis or EUS much more accurate at evaluating locoregional stage than CT scan, although CT chest/abdomen essential to identify metastases.
- Treatment decisions should be made with reference to ➔ TNM classification rather than Dukes staging. American Joint Committee on Cancer has designated:
  - Stage I: T1 or T2, N0, M0.
  - Stage II: T3 or T4, N0, M0.
  - Stage III: Any T, nodal involvement, M0.
  - Stage IV: Distant metastases.

Management

Surgery

- Resection indicated for removal of primary tumour and regional lymph nodes for localized disease.
- Transanal excision (TAE) can be used for early cancers confined to rectal submucosa. Technique can affect rate of local recurrence.
- Total mesorectal excision with colo-anal anastomosis associated with low incidence of local recurrence (4%), but risk of anastomotic dehiscence up to 15%.
- Abdominoperineal resection with end-sigmoid colostomy indicated in patients with lower-third rectal cancers who cannot undergo sphincter-saving procedure because there is <2cm disease-free distal margin.
- Transanal endoscopic surgery (TES) is an emerging technique for early-stage rectal cancers. Offers improved visualization and access, and associated with lower rates of local recurrence than TAE.

Adjuvant therapy

Because of ↑ risk of local recurrence (up to 50% for stage II-III disease), perioperative radiation has greater effect in rectal than ➲ colon cancer. Pre- and postoperative radiation therapy ↓ risk of recurrence in stage II-III, but ↑ patient survival not been shown. Because preoperative radiotherapy delays surgery and makes pathological staging difficult, postoperative radiotherapy may be preferable. Combined therapy with 5-FU and radiation widely used for stage II and III disease, but further studies needed to determine long-term results.

Palliative and experimental treatments

Endoscopic therapy using Nd:YAG ➢ laser can recanalize rectum in patients with obstructing cancers who are unfit for surgery. Mesh metal stenting and photodynamic therapy have been used in small numbers of patients.

Prognosis

Overall 5y survival rates 72% for stage I, 54% for stage II, 40% for stage III, and 7% for stage IV.

Guideline

NICE guideline on the diagnosis and management of colorectal cancer (2014) 🖱 https://www.nice.org.uk/guidance/CG131.

Rectal prolapse

Intussusception of rectum through anal canal can vary from rectal mucosa only to full thickness of rectum and sigmoid colon.

Causal factors

- Neurological or muscular disease leading to pelvic floor weakness.
- Impaired function of anal sphincters.
- Chronic constipation with resultant straining.
- Colorectal tumours.

Clinical features and diagnosis

Presenting symptoms may include pain, incontinence, or sensation of 'something coming down'. Demonstration can be helped by having patient strain in sitting position or by ➢ defaecography. Proctoscopy important in excluding internal haemorrhoids and anal tumours. Colonoscopy to exclude tumour indicated, as is complete pelvic floor examination as risk of associated bladder or uterine prolapse. ➢ Anorectal manometry, with pudendal nerve function testing, may be necessary because nerve can be injured by chronic traction by prolapse.

Treatment

- Surgery central to management.[2] Many different procedures depending on age and aetiology. Both abdominal (anterior repair and rectopexy) and perineal (usually resection of prolapse, possibly with pelvic floor repair) approaches possible.
- Medical management offered to ↓ symptoms in patients unfit for, or who decline, surgery. These include adequate fluid and fibre intake.
- Enemas and suppositories can be helpful with severe constipation.
- Pelvic floor exercises may be helpful in some ♀.

Rectal ulcer

See: ➔ Solitary rectal ulcer syndrome.

Rectocoele

In ♀, the anterior rectal wall above perineal body is unsupported, and the rectovaginal septum may bulge anteriorly to form a rectocoele (Fig. 4.19). Can give symptoms of incomplete evacuation of stool, lump appearing at introitus with straining, and sometimes having to support posterior vaginal wall with finger or thumb or digitally evacuate stool to enable defaecation. Rectocoele most easily demonstrated on ➢ defaecography study. Surgical repair can be done via endorectal, transvaginal, or transperineal approaches, and beneficial in ≈75% of selected patients.

Refeeding syndrome

Aetiology and pathogenesis

Metabolic complication, occurring when nutritional support is given to severely malnourished patients. Insulin secretion ↓ during periods of insufficient nutrition because of ↓ carbohydrate intake. Fat and protein are instead catabolized to produce energy. Results in intracellular loss of electrolytes, particularly phosphate.

Clinical features

Re-initiation of feeding results in ↑ insulin, which stimulates glycogen, lipid, and protein synthesis. These processes further deplete phosphate, magnesium, and thiamine; drive potassium intracellularly; and establish osmotic gradients that promote fluid shifts (see Box 4.70). Usually occurs within 4d of refeeding. Serum phosphate <0.5mmol/L can produce clinical features of rhabdomyolysis, leukocyte dysfunction, respiratory failure, cardiac failure, hypotension, muscle weakness, arrhythmias, and seizures. Refeeding syndrome can occur with parenteral or enteral feeding. Criteria for identifying high-risk patients:

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[2] Hotouras A *et al.* (2015). *Colorectal Dis* **17**: 657–64.

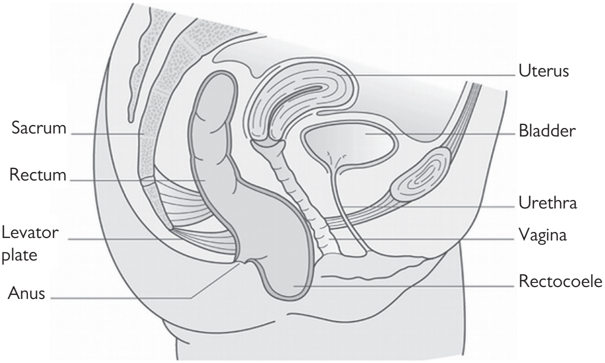

Fig. 4.19 Formation of a rectocoele.

- Either 1 or more of:
  - BMI <16kg/m² (see also ➲ anorexia nervosa).
  - Unintentional weight loss >15% within 6mo.
  - Little or no nutritional intake for >10d.
  - ↓ levels of potassium, phosphate, or magnesium.
- Or 2 or more of:
  - BMI <18.5 kg/m².
  - Unintentional weight loss >10% within 6mo.
  - Little or no nutritional intake for >5d.
  - History of ➲ alcohol dependency or cancer.
  - Medications including insulin or chemotherapy.

Box 4.70 Clinical features of refeeding syndrome

- Hypokalaemia.
- Hypomagnesaemia.
- Hypophosphataemia.
- Disordered sodium balance.
- Fluid shifts.
- Hypocalcaemia.
- ➲ Wernicke's encephalopathy.

Management

- For patients meeting high-risk criteria, nutritional support should be started at a maximum of 10kcal/kg/d, increasing slowly to meet full requirements by d4–7.
- Patients who have eaten little or nothing for >5d should have nutritional support introduced at no more than 50% of requirements for first 2d, before increasing feed rates to meet full needs (so long as clinical and biochemical monitoring reveal no refeeding problems).

- In patients who are at high risk of developing refeeding syndrome, ➔ vitamin B supplementation should be given immediately before and during first 10d of feeding: oral thiamine 200–300mg/d + vitamin B Co Strong 1–2 tablets tds, or Pabrinex® 2 pairs IV tds for 2d.
- For phosphate replacement, give 50mmol IV over 24h. Correct other electrolytes as required (see ▶ Approach to electrolyte disturbance): NICE recommend 0.3–0.6mmol/kg/d phosphate, 2–4mmol/kg/d potassium and 0.2–0.4mmol/kg/d magnesium, unless pre-feeding levels high.[3] Monitor electrolytes and ECG daily for 1wk, then 3 times the following week. Examine daily for fluid overload or confusion.
- Acute vitamin and mineral deficiencies can also be precipitated by feeding without appropriate micronutrients. ➔ Folate deficiency can result in megaloblastosis and thrombocytopaenia, and ➔ vitamin B_{12} deficiency in lactic acidosis.

Reiter's syndrome

See: ➔ Reactive arthritis.

Retroperitoneal haemorrhage

Rare, but potentially life-threatening. Consider in patients who appear to be bleeding without obviously detectable source. Risk factors:

- Leaking abdominal aneurysm.
- Haemorrhagic pancreatitis.
- Trauma.
- Cardiac catheterization using femoral access.
- Adrenal malignancy.
- Anticoagulation or bleeding diathesis (e.g. haemophilia).

Patient may be shocked, with abdominal or flank pain, although signs of haemorrhage can initially be subtle. Peri-umbilical (Cullen's sign) or flank (Grey-Turner's sign) bruising may be present, although occur late. If severe, abdominal compartment syndrome can develop, defined as intra-abdominal (usually measured as intravesical) pressure >200mmHg. Manifests with renal failure, reduced cardiac output, respiratory failure, and intestinal ischaemia.

Patient survival depends on rapid diagnosis, restoration of circulatory volume (activate ▲ **major haemorrhage protocol** ▲). CT is the investigation of choice; IV contrast not required to establish diagnosis, but does help detect active extravasation. US, including FAST scan (see ▲ **Abdominal trauma** ▲), not useful. Treatments include transcatheter arterial embolization to stop ongoing bleeding, or surgical haemostasis. Surgical decompression of haematoma required if compartment syndrome present.

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[3] Hearing SD (2004). *BMJ* **328**: 908–9.

Retroperitoneal perforation

- Perforation of abdominal viscus into retroperitoneum may occur spontaneously (colonic ➲ diverticular disease, posterior ➲ duodenal ulcer), or be iatrogenic (complicates <1% of biliary sphincterotomies, see ➢ 'ERCP', p. 210 and ➢ 'colonoscopy', p. 215; and also following rectal instrumentation).
- Air may rapidly track into mediastinum and soft tissues, presenting with subcutaneous emphysema, soft tissue swelling, and skin crepitus on palpation (like squeezing bubble wrap). May be recognized by air outlining kidney, bowel, or psoas muscle on plain X-ray, but CT confirms diagnosis. If not noted at time of ERCP, may present the following day with abdominal pain suggestive of ➲ acute pancreatitis, but without significantly raised amylase.
- Treatment includes strict NBM, IV fluids, and broad-spectrum antibiotics (e.g. third-generation → CEPHALOSPORIN and → METRONIDAZOLE). Surgery rarely necessary for sphincterotomy perforation, but still involve the surgical team early. Significant morbidity related to retroperitoneal abscess formation, which requires percutaneous drainage and surgery. Large colorectal tears may require surgery.

Rheumatoid arthritis and the GI tract

GI manifestations of rheumatoid arthritis

- Temporomandibular arthritis present in up to 50%. Can cause pain and crepitus on chewing.
- Oesophageal dysmotility results from low-amplitude peristalsis and ↓ lower oesophageal sphincter pressure.
- Vasculitis affects 1% of rheumatoid patients, of whom 10–38% have GI involvement. Clinically apparent disease rare but, when manifests, often serious. Diagnose on biopsy (small vessel) or angiography (large vessel).[4]
  - Arteriolitis causes multiple ischaemic ulcers and perforation.
  - Arteritis causes segmental colitis ± intraperitoneal haemorrhage from aneurysm rupture. May heal with stricturing.
  - May mimic ➲ appendicitis.
  - Treatment usually involves → CORTICOSTEROIDS ± cyclophosphamide, as well as interventional radiology or surgery to manage severe complications.

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[4] Ebert EC & Hagspiel KD (2011). *Dig Dis Sci* **56**: 295–302.

- ➲ Amyloidosis can cause ➲ pseudo-obstruction or malabsorption (see ▶ Approach to malabsorption and steatorrhoea). Duodenum most commonly affect. Management involves control of underlying chronic inflammatory disease.
- See also ➲ Felty's syndrome and ➲ Still's disease.

GI problems of drug therapy for rheumatoid arthritis

- Endoscopic lesions seen in 20–40% of rheumatoid patients who take NSAIDs. Risk ↑ by age >60y, history of peptic ulcer, use of steroids, and extra-articular manifestations.
- In past, use of gold associated with GI toxicity, especially colitis.
- Sulfasalazine can cause pancreatitis.
- → METHOTREXATE causes hepatic fibrosis in cumulative doses >1.5g.

Rockall score

See: ➲ Scoring systems for predicting outcomes in GI bleeds.

Rotavirus

Non-enveloped dsRNA reovirus, first described in 1973. Groups A-C reported as pathogens in human; most disease caused by group A. Causative agent for much of non-bacterial gastroenteritis, particularly in children. May cause outbreaks. Person-to-person spread via faeco-oral route. After ingestion, virus particles invade enterocytes in small intestine and cause cytolysis. Highly infectious (up to 10^{11} virus particles shed/g faeces in children). Patients with immune deficiency at particular risk. Typically presents with fever and vomiting for 2–3d, followed by non-bloody diarrhoea for further 1–4d. Stool generally devoid of faecal leukocytes. Diagnosis now principally by viral PCR, which can be performed on stool or vomitus. Treatment aimed at correcting fluid and electrolyte disturbances, ideally with ➲ oral rehydration solution; IV therapy should be reserved for those in whom oral route insufficient to meet requirements. See also: ▶ Approach to acute diarrhoea. Vaccine now available for children age <2y.[5]

Rotor syndrome

Autosomal recessive condition. Similar to ➲ Dubin–Johnson syndrome, except on liver biopsy no accumulation of black pigment in liver parenchyma is seen in Rotor syndrome. Conjugated hyperbilirubinaemia due to impaired excretion. Presents with mild jaundice but normal liver function. No specific treatment, and good prognosis.

[5] Tate JE & Parashar UD (2014). *Clin Infect Dis* **59**: 1291–301.

Roundworm (nematode) infection

Think of four groups.

Infection confined to human GI tract

Organisms include *Trichuris* (see ➔ whipworm), *Enterobius* (pinworm), *Capillaria* (important in Philippines and Far East), and *Trichostrongylus* (human infection most prevalent in Middle East and Asia).

Enterobius vermicularis (pinworm)

Infestation common in developed countries. Often occurs in family clusters, independent of home sanitary conditions. Faeco-oral acquisition via hand-mouth contact or fomites (e.g. clothes, toys). No animal reservoir. Eggs hatch in duodenum within 6h ingestion, mature within 2wk, and have lifespan of 2mo. Adult worms live free in lumen of terminal ileum, caecum, and proximal ascending colon, and do not invade healthy mucosa. Female worms migrate to rectum after copulation and, if not expelled during defaecation, lay eggs on perineal skin (often at night, with average of 11,000 eggs released). These become infectious within 6-8h, and remain so in environment for up to 3wk. Because of short incubation, eggs deposited under fingernails during scratching then placed in mouth may cause cycle of reinfestation.

Patients are often asymptomatic, but most common symptoms if they emerge are ➔ pruritus ani and pruritus vulvae. Diagnosis confirmed by visual report of worm, or identifying eggs (press wide adhesive tape against perineum at night or in morning to capture eggs, then examine 3 consecutive specimens under low power microscope). Treat with mebendazole 100mg or albendazole 400mg PO single dose, repeated 2wk later if infection ongoing.

Infection begins in GI tract: larvae invade and reach lungs, migrate to pharynx, swallowed, and mature in gut

Ascaris lumbricoides

Adult worms can be 10–25cm long. Infection common (1.2 billion worldwide, only cold dry climates spared) but worm burden varies considerably; some individuals harbour massive infestations and act as reservoir. Ingested ova hatch in small intestine and migrate to caecum/proximal colon where penetrate mucosa. Travel to liver via portal circulation, then advance to lungs, and invade alveolar space. Subsequently travel up oropharynx, where swallowed and return to small intestine. Hepatotracheal migration takes place from 8 to 10d post-infection. Clinical features can result from migration of larvae through lungs (bronchospasm, bronchiolar inflammation, Löffler syndrome, urticaria, or other manifestations of hypersensitivity) or (in heavy infections) by blocking gut or biliary tree. Diagnosis by finding eggs in stool, larvae in sputum samples (if hypersensitivity pneumonitis), or worms in GI/biliary tract. Treat with mebendazole 500mg or albendazole 400mg PO single dose. Mechanical removal of worms at ERCP may be required if ➔ cholangitis or ➔ acute pancreatitis.

Larvae invade skin, migrate to lungs, then swallowed and mature in gut

Hookworms and ➔ Strongyloides (see separate section in A-Z).

Ancylostoma duodenale and Necator americanus (hookworm)

Common, infecting 440 million people worldwide. Acquired through skin exposure to larvae in soil contaminated with human faeces. Migrate to lungs, then up to oropharynx, swallowed, and mature in small intestine. Adult worms secrete hyaluronidase (degrades intestinal mucosa causing extravasation) and anticoagulant, resulting in iron-deficiency anaemia in 10% of those infected. Spread facilitated by walking barefoot and using human faeces as manure. Worms do not multiply within host, therefore if not re-exposed infection disappears after worm dies (*A. duodenale* ≈1y; *N. americanus* 3-5y). Majority asymptomatic, but clinical features can include:

- Ground itch. Pruritic rash at site of skin penetration.
- Pulmonary hypersensitivity reaction/Löffler syndrome (≈1wk after exposure).
- Iron-deficiency anaemia.
- Protein malnutrition (↓ albumin).
- Peripheral blood eosinophilia (common).

Diagnosis made by finding eggs in stool, or adult hookworms on endoscopy. Treat with mebendazole 100mg bd for 3d, or albendazole 400mg single dose. Provide iron supplementation where needed. Complete prevention requires improvements in public sanitation. Wearing footwear reduces, but does not eliminate, risk.

Intestinal nematodes of animals that can infect humans

Trichinella spiralis (trichinellosis/trichinosis)

Acquired from poorly cooked meat. Incubation 8-15d. Larvae burrow into gut wall and migrate to skeletal muscle; extraocular muscles often affected. Initial symptoms most commonly GI (particularly diarrhoea). Subsequently, 75% develop myalgia (particularly masseter and intercostals) and muscle weakness (often pain-related rather than true loss of power). Palpebral oedema can be characteristic. Most severe manifestation is cardioneurologic syndrome, which presents with encephalopathy, focal neurologic deficits, or acute myocardial injury (myocarditis, sinus or atrial node dysfunction, heart failure, or infarction). Diagnosis serological (ELISA for IgG; positive within 2wk though some cross-reactivity) or (rarely) muscle biopsy. Almost all patients have ➔ eosinophilia. CK ↑ in 90% once muscle invasion begins and urinalysis may reveal myoglobinuria. Plain radiographs can reveal calcified densities in muscles, indicating old disease, but do not help evaluate acute infestation. CT or MRI useful for those with neurological symptoms. ECG required to exclude cardiac rhythm disturbance. Treat with albendazole 400mg od for 14d. → CORTICOSTEROIDS may have role if neurological or myocardial involvement present.

Ancylostoma braziliense (cutaneous larva migrans)

Serpiginous pruritic dermatitis. Found in Africa, Caribbean, and Latin America. Hookworms of dogs and cats burrow through skin. Treat with ivermectin 200μg/kg stat or albendazole 400mg od for 3d.

Toxocara canis/cati (visceral larva migrans)

Results from ingestion of *Toxocara* eggs living in dogs or cats. Larvae penetrate intestine but cannot complete life-cycle in humans and migrate through various organs. Clinical course highly variable. Classical triad is ➲ eosinophilia, hepatomegaly, and hypergammaglobulinaemia. May develop fever, cough, wheeze, Löffler's syndrome, abdominal discomfort, and splenomegaly. ELISA detects anti-*Toxocara* antibodies (sensitivity 78%, specificity 92%). CT shows pulmonary infiltrations if respiratory involvement, or abnormal parenchyma with hepatic involvement, and MRI multiple cerebral lesions in CNS disease. Occasionally tissue biopsy required if diagnostic uncertainty: multiple eosinophilic abscesses and granulomas often found, but negative biopsy does not exclude. Treat with albendazole 400mg PO bd for 7d. Consider → CORTICOSTEROIDS if myocarditis or CNS disease.

Anisakiasis

Caused by nematode pathogens of fish. Occurs if contaminated fish or squid eaten raw or undercooked. Highest prevalence in Scandinavia (from cod liver), Japan (sushi and sashimi) and Pacific coast of South America (ceviche). Mucosal invasion of stomach causes severe gastritis or profuse haemorrhage within 12–24h of ingestion. Diagnosis can be confirmed on OGD, where 2cm larvae may be observed and removed. Worms cannot survive in humans, and in most cases only symptomatic treatment is required. Rarely, large worm bolus can cause small bowel obstruction, in which case surgery may be necessary.

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Salmonella

Gram-negative bacillus causing food-borne infection, transmitted by 'flies, fingers, food, faeces, and fomites'. Recent pandemics in Western countries due to infection of commercial eggs and poultry. *Salmonella* penetrates ileum and colon, with haematogenous dissemination to other organs. Five clinical syndromes (Box 4.71). *S. typhi* and *paratyphi* cause enteric fever; remainder (*enterica* species) cause gastroenteritis. Risk ↑ by haemolytic anaemia, leukaemias, lymphoma, cancer, steroids, chemotherapy, gastric surgery, acid suppression, and ➔ schistosomiasis. Up to 6/1,000 patients become chronic asymptomatic carriers; this is strongly associated with the presence of gallstones (present in ≈90%).

Box 4.71 Clinical syndromes of *Salmonella* infection

- **Gastroenteritis** (75% of infections).
- **Enteric fever** (10%).
- **Bacteraemia** Associated with endocarditis and arteritis (10%).
- **Localized infection** Bones/joints, meninges, mycotic aneurysms (5%).
- **Carrier state**.

Gastroenteritis

Incubation 6–48h. Nausea, vomiting, abdominal cramps, and diarrhoea last 3–4d; latter can vary from few loose stools to dysentery. Fever in 50%. As with ➔ *Campylobacter*, risk of developing ➔ reactive arthritis and post-infectious ➔ irritable bowel syndrome. Systemic infection in 5%, but carries mortality up to 25%.

Enteric fever

Caused by *S. typhi* and *S. paratyphi* A, B & C. Endemic in SE Asia, where incidence 100/100,000; typically imported in developed countries. Cases of paratyphoid are on the increase. Presents with protracted fever, abdominal discomfort, nausea, malaise, and headache. Textbook signs include relative bradycardia (<50%) and rose spots (rare but pathognomonic). May get Peyer's patch enlargement (can bleed or perforate), lymphadenopathy, and hepatosplenomegaly. 10% develop serious complications, and mortality 1%.

Diagnosis

- **Gastroenteritis** Stool MC&S in patients with gastroenteritis.
- **Systemic upset/suspected enteric fever:**
  - Blood (although negative in ≈40%).
  - Bone marrow sampling and culture if diagnostic uncertainty.[1]

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[1] Waddington CS *et al.* (2014). *J Infect* **68**: S38–50.

Treatment

Gastroenteritis

- Most patients with uncomplicated infection should not have antibiotics as usually self-limiting while risk emergence of resistant strains.
- Indications for treatment include associated malignancy, immunosuppression, cardiovascular abnormalities, and presence of orthopaedic prostheses. Aim is to prevent bacteraemic disease.
- Quinolones, such as → CIPROFLOXACIN, usual 1st line antibiotic, but evidence of ↑ drug resistance (so check sensitivities).

Systemic disease/enteric fever

- 3rd and 4th generation → CEPHALOSPORINS (e.g. ceftriaxone 2g IV od) eliminate bacteraemia fastest. However, as *Salmonella* can seek refuge within reticuloendothelial cells, recurrence lowest with azithromycin (which accumulates intracellularly).
- → CIPROFLOXACIN can be used for non-severe disease.
- Two vaccines currently commercially available for typhoid fever:
  - Vi polysaccharide capsular vaccine. Protective in 70% for up to 3y; safe in immunocompromise.
  - Ty21 highly attenuated oral vaccine. Administered as 3 doses, alternate days. Efficacy 60–70%, for up to 70y.[2]

Asymptomatic carriers

- Prolonged antibiotic therapy (up to 28d) results in cure rates >80%.
- Additive benefit of cholecystectomy to eliminate gallstone nidus of infection.[3]

Sarcoidosis

Systemic granulomatous disease of unknown aetiology. Affects liver in up to 15% of cases, and important cause of ➲ hepatic granulomas. Stomach is the most commonly affected part of GI tract.

Clinical features

- More common in Afro-Caribbeans than Caucasians.
- Often asymptomatic, with incidental LFT abnormalities in patients with symptomatic lung, skin, or eye disease.
- Hepatomegaly, fever, and RUQ quadrant discomfort may occur.
- Rare presentations include severe intrahepatic cholestasis; ➲ portal hypertension due to cirrhosis/granulomas; and extrahepatic biliary obstruction due to portal lymph nodes, bile duct inflammation, and pancreatic sarcoid with distal ➲ biliary stricture.

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[2] Martin LB (2012). *Curr Opin Infect Dis* **25**: 489–99.

[3] Gunn JS *et al.* (2014). *Trends Microbiol* **22**: 648–55.

Investigation

- LFTs often show ↑ ALP/GGT and mildly ↑ AST/ALT. When previous diagnosis of sarcoid not made, ↑ serum angiotensin-converting enzyme (sACE) and lung changes (e.g. bilateral hilar lymphadenopathy) may aid diagnosis.
- CT/US findings non-specific, but granulomas can occasionally coalesce to form 0.5–3cm nodules.
- ➢ Liver biopsy shows non-caseating granulomas in >80%, commonly along portal tract. Cirrhosis on biopsy in 6%.

Management

- → URSODEOXYCHOLIC ACID may improve symptoms in intrahepatic cholestasis.
- Oral → CORTICOSTEROID therapy induces clinical and biochemical remission in biopsy-proven granulomatous hepatitis. Duration of use uncertain, but high relapse rate with short-term treatment.
- Immunosuppression less effective in established cirrhosis and portal hypertension. Rarely, ➲ liver transplantation may need considering.

Schatzki ring

See: ➲ Oesophageal ring.

Schilling test

See: ➢ 'Schilling test', p. 151.

Schistosomiasis (bilharzia)

Epidemiology and pathogenesis

- Schistosomes are trematode blood flukes. >240 million people are chronically infected worldwide. Endemic areas include Africa, South America, Far East, and SE Asia.
- Intestinal and hepatosplenic schistosomiasis are caused by *S. mansoni*, *japonicum*, *intercalatum*, and *mekongi*. *S. haematobium* causes urinary disease.
- Life cycle maintained in mammalian definitive hosts; freshwater snail is the intermediate host. Humans acquire infection following direct contact with water sources containing cercariae. Larvae penetrate skin, transform into schistosomula, and mature in circulation. During migration, found in lungs in large numbers, as held up in capillary bed. Enter portal system, where ♂ and ♀ worms sexually mature and pair up, after which migrate to mesenteric or vesical venous plexuses (depending on species). Eggs excreted via faeces or urine, from which free-swimming miracidia emerge, infect freshwater snails, and develop into cercariae.[4]

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[4] Colley DG *et al.* (2014). *Lancet* **383**: 2253–64.

- Adult worms colonize blood vessels for years, evading immune system while excreting thousands of eggs daily. These are excreted, or retained in nearby tissues, eliciting granulomatous response. In liver, this leads to ➔ portal hypertension ('pre-sinusoidal'), although not cirrhosis.

Clinical features

- **Swimmers itch** Immune-mediated dermatitis at site of cercarial skin penetration. Presents with pruritic maculopapular rash lasting <1wk.
- **Acute schistosomiasis (Katayama fever)** Develops 3–6wk after primary infection as a result of host immune response to migrating worm and egg production. Usually asymptomatic, but can manifest with fever, malaise, abdominal pain, diarrhoea, and eosinophilia.
- Only small proportion of **chronically infected** people suffer significant clinical problems:
  - Features primarily due to periportal ('Symmer's pipe-stem') fibrosis and ➔ portal hypertension. Develop varices, hepatosplenomegaly, and ascites. Stigmata of chronic liver disease and liver failure rare, and as result bleeding from gastro-oesophageal varices carries better outcome than in those with cirrhosis.
  - In some areas, frequent co-infection with ➔ hepatitis B/C (see Box 4.72).
  - Recurrent abdominal pain, bloody diarrhoea, gut microabscesses, and colonic polyposis manifesting as ➔ protein-losing enteropathy may also occur.
  - Rarely get ectopic deposition of schistosoma eggs (e.g. in CNS). Can present as encephalopathy, meningoencephalitis, transverse myelitis, or spinal cord compression.

Investigation

- Peripheral eosinophilia characteristic of acute infection.
- ↑ ALP and GGT often seen.
- Stool microscopy. Ova characteristic (with lateral or terminal spine), but usually absent in acute infection. Kato-Katz thick stool smear simple and specificity 100%, but loses sensitivity in low intensity infection.[5] Yield improved by repeated samples and sigmoidoscopic biopsies.
- ELISA for serum antibodies against soluble worm or egg antigens confirms exposure (and if negative reliably excludes chronic infection), but not useful in distinguishing past from ongoing infection. Positive serology develops after acute infection.
- Schistosomal liver disease may be suggested by US findings: classical features include 'bulls-eye' lesions, network echogenic pattern, granulomas, and gallbladder thickening. If present, these are pathognomonic and ∴ liver biopsy not usually indicated. CT and MRI can also be used but not routine in resource-poor areas. If diagnostic doubt, ➤ liver biopsy definitive.

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[5] Weerakoon KG *et al.* (2015). *Clin Microbiol Rev* **28**: 939–67.

Management

- Praziquantel 40mg/kg PO for 1d for *S. mansoni* (↑ to 60mg/kg for *S. japonicum* and *mekongi*) clears infection in 60–95%, with ↓ in egg burden in remainder. Efficacy 95–100% if dose repeated 4–6wk later. May prevent progression of chronic infection, but does not reverse portal hypertension.
- Prednisolone 1.5–2mg/k/d used to treat Katayama syndrome.
- ➲ Portal hypertension may require standard management of complications (e.g. primary/secondary prophylaxis).

Box 4.72 Schistosomiasis, hepatitis C, and public health

Up to 15% of Egyptian population are infected with ➲ hepatitis C. This extraordinarily high rate may be linked to mass population programme for schistosomiasis eradication in 1960s and 1970s. Sadly, treatment with parenteral antischistosomal therapy (PAT) was often given using multiply used, poorly sterilized needles.

Sclerosing cholangitis

See: ➲ Primary sclerosing cholangitis.

Sclerosing mesenteritis

Also known as mesenteric lipodystrophy or panniculitis. Rare condition characterized by mesenteric fat degeneration and necrosis, which progresses through chronic inflammation to fibrosis. Autoimmune aetiology presumed, and in some cases associated with IgG4-related systemic disease. ♂:♀ = 2:1. Onset typically in 5th–7th decade. Can be asymptomatic (identified incidentally on imaging), but may cause abdominal pain, nausea and vomiting, bloating, change in bowel habit, and (in severe cases) ▲ **bowel obstruction** ▲. Constitutional symptoms (fatigue, low grade pyrexia) common. Inflammatory markers may be elevated. Diagnosis suggested on CT/MRI, which shows thickening of mesentery ± lymph node enlargement. Biopsy required to secure diagnosis and fully exclude neoplastic infiltration if any uncertainty following imaging.

No treatment required if asymptomatic, but otherwise case reports and small series suggest efficacy of → CORTICOSTEROIDS, colchicine, → AZATHIOPRINE, → THALIDOMIDE, and → INFLIXIMAB.

Scoring systems for predicting outcomes in GI bleeds

Several risk scoring systems have been developed to predict re-bleeding and death in patients with ▲ **acute upper GI bleeding** ▲ (see this entry also for score tables).

- **Blatchford score** 🖱 https://www.mdcalc.com/glasgow-blatchford-bleeding-score-gbs. Designed to discriminate patients who need clinical intervention from those who do not. Does not rely on endoscopic findings. Patients with score <1 can be investigated as outpatient, provided no other factors (comorbidity, social circumstances) limit ambulatory management. Score ≥5 carries at least 50% probability of requiring endoscopic intervention.
- **Rockall score** 🖱 https://www.mdcalc.com/rockall-score-upper-gi-bleeding-complete. Validated mortality risk assessment, with some predictive value for risk of re-bleeding. Good for identifying patients who may be suitable for early discharge post endoscopy (score <2).
- **Forrest classification** 🖱 https://www.qxmd.com/calculate/calculator_92/forrest-classification. (Table 6.6 and Plate 16). Describes endoscopic signs indicating risk of re-bleeding from peptic ulcer. Based on untreated lesion.
- Other scores exist, but these are the most validated and useful in practice.

Sengstaken–Blakemore tube (SBT)

Background

- Bleeding from gastro-oesophageal (GO) varices is primarily controlled by endoscopic and pharmacological therapy (see acute variceal bleeding in ▲ **Acute upper GI bleeding** ▲ and ➲ portal hypertension). If these approaches are ineffective or unavailable, mechanical compression should be instituted.
- SBT insertion is one of the most effective emergency interventions in gastroenterology—**done right it saves; done wrong it may hasten patient's demise.** Configuration shown in Fig. 4.20.

Technique

- Essential to be fully prepared before attempting SBT insertion. Should be performed by an experienced clinician.
  - HDU/ITU setting.
  - Enrol senior nursing/medical staff if available.
  - Patient should undergo endotracheal intubation to protect airway.
- Mouthpiece in, lubricant jelly on SBT. Left forefinger between mouthpiece and side of mouth to guide tube. Slow steady insertion to limit of tube.
- Inflate gastric balloon to 250ml with mixture of water and Omnipaque using 50ml bladder syringe, then seal balloon port with two clamps. This should not elicit distress (if does, may suggest gastric balloon in oesophagus—risk of ▲ **oesophageal rupture** ▲).

- Slow traction on tube, expecting resistance at ~35cm from teeth.
- Secure tube to side of mouth, under light tension. To do this, first release the mouthpiece and leave on tube near ports. Maintaining traction, place 2 wooden tongue depressors either side of tube at mouth, at 90° to line of tube. Use Elastoplast to secure firmly together and around tube. Place piece of gauze between tongue depressors and side of mouth to prevent trauma. Mark tube to detect slippage.
- Check CXR (see gastric balloon in stomach, with 'nipple effect' due to slight traction into distal oesophagus).
- Aspirate oesophageal port quarter-hourly, gastric port half-hourly.
- Aim to deflate and remove SBT within 12h and re-scope/watch response.
- SBT can be inserted under direct endoscopic vision: with gastroscope in stomach, advance SBT down oesophagus into stomach. Gastric balloon can then be inflated as described, thereby reducing risk of inflation within oesophagus.

Lack of control of bleeding

- May be due to:
  - Ineffectively deployed SBT + gastric balloon. Attempt repositioning (Box 4.73).
  - Varices feeding into mid-oesophagus (i.e. not controlled by pressure at GO junction). May be treated by inflating oesophageal balloon (although significantly ↑ risk of oesophageal necrosis and rupture). Inflate balloon to ≈40mmHg (sphygmomanometer can be useful here), but let down every 1–2h for 5–10min to minimize risk of necrosis.
  - Gastric or ectopic varices.
- Contact liver centre and consider emergency ➲ TIPSS.
- Fully covered self-expanding metal stents, specific for management of variceal bleeding, can be used as an alternative to SBT or TIPSS.

Seton suture

Suture, wire, or tubing used in surgical management of anorectal fistulae (e.g. in ➲ perianal Crohn's disease). Threaded through fistulous tract and secured outside anus, usually with knot. Can be left loose to allow drainage and subsidence of local infection, or tied tightly to slowly cut through muscle—in theory maintaining muscle fibre alignment, allowing healing, and preventing abscess formation.

Box 4.73 Practice point: Forget the fridge!

Time-honoured advice for SBT insertion is to put the tube in a fridge beforehand. Even in non-intubated patient, this apparently ensures that cool stiffened tube gently glides into position without difficulty. Great, except it doesn't work. By the time the tube has been in your warm sweaty hands for 10s, all stiffness has been lost. Safe, effective SBT insertion achieved by having patient intubated beforehand.

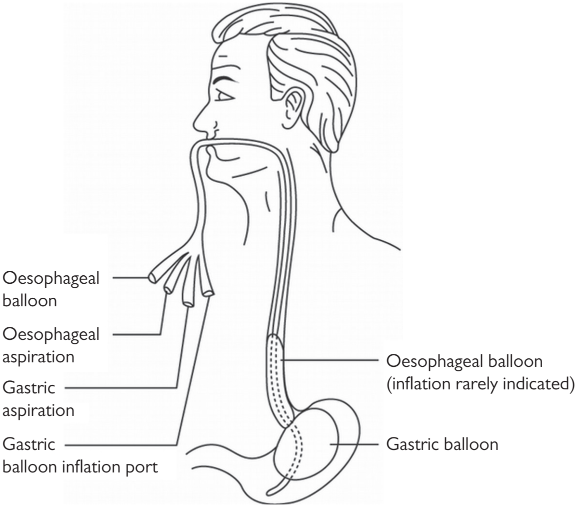
Oesophageal balloon
Oesophageal aspiration
Gastric aspiration
Gastric balloon inflation port
Oesophageal balloon (inflation rarely indicated)
Gastric balloon

Fig. 4.20 Sengstaken–Blakemore tube in place.

Shigella

Important cause of bacterial dysentery and ➔ food poisoning. Prevalent in N Africa and SE Asia. No natural reservoir but highly contagious; spread person-to-person or through contaminated food. Invades colon and terminal ileum. Bacteraemia rare. Four species cause human disease: *S. dysenteriae,* (most severe), *S. flexneri, S. boydii*, and *S. sonnei* (mildest).

Clinical features

Lower abdominal pain, rectal discomfort, and diarrhoea (bloody in one-third). Fever in 40%. Complications include intestinal perforation, ➔ reactive arthritis (usually HLA-B27-associated), and (rarely) ➔ haemolytic-uraemic syndrome. Infection shorter in children (1–3d) than adults (≈7d).

Diagnosis

- Send stool for MC&S.
- Sigmoidoscopy not usually required, but if performed shows colitis; biopsy may support infective cause rather than ➔ ulcerative colitis.

Treatment

Antibiotics often not needed but reasonable if diarrhoea persisting by time of positive stool cultures. Quinolones (e.g. → CIPROFLOXACIN 500mg PO bd for 3d) 1st line. Resistance generally <1%, but if in area where more prevalent use azithromycin 500mg PO od for 3d. Avoid opiates.

Short bowel syndrome

Malabsorption syndrome resulting from extensive intestinal resection. Major underlying causes in adults are ➲ Crohn's disease, mesenteric infarction, and ➲ radiation injury. Degree of malabsorption related to remaining length of small and large bowel. Nutrient absorptive capacity higher in proximal small intestine than distal small bowel (Box 4.74).

- Water and electrolyte malabsorption. Net sodium and fluid balance related to jejunal length (measured from duodenojejunal flexure). ➲ Intestinal failure can be avoided if >50cm jejunum remains with colon in continuity. These patients require a high carbohydrate (polysaccharides), low oxalate diet.
- For patients with jejunostomy, if <100cm of jejunum remains, parenteral saline (and if <75 cm, ➲ parenteral nutrition) likely to be needed in long term.
- In these patients, use of ➲ oral rehydration solutions (with sodium concentration 90–120mM) can ↓ stoma output and convert some patients from net secretors to net absorbers of sodium and fluid. ❗ Sport drinks and commercially-made liquid formula feeds contain too little sodium for maximal fluid absorption in patients with short bowel and jejunostomy.
- Jejunal output may be further ↓ by drugs that ↓ motility (→ LOPERAMIDE) or ↓ gastric secretion (→ H_2 RECEPTOR ANTAGONISTS, → PROTON PUMP INHIBITORS).
- Calcium and magnesium are absorbed in duodenum and proximal jejunum. Hypomagnesaemia is common and treated by correcting sodium depletion, oral or IV magnesium supplements, and ensuring patients are vitamin D replete. Be aware that oral magnesium can increase stoma output/diarrhoea and thus can worsen hydration and nutritional status.
- Ileal resection >50cm frequently impairs ➲ vitamin B_{12} absorption, and resection of >100cm causes ➲ bile acid malabsorption.

Box 4.74 Complications of short bowel

- Cholesterol gallstones. ↓ hepatic bile acid secretion leads to cholesterol supersaturation.
- Renal ➲ oxalate stones.
- D-lactic acidosis. If colon *in situ*, monosaccharide carbohydrate overfeeding can result in excess ➲ short-chain fatty acids. Lowers colonic pH, promoting Gram-positive anaerobes that produce D-lactate. Humans lack D-lactate dehydrogenase. Absorbed D-lactate may cause nystagmus, ataxia, and confusion. Patients look drunk but blood alcohol normal; D-lactate levels high (>3mM/L).

Guideline

🖱 BSG guideline for management of patients with a short bowel (2006).

Short-chain fatty acids (SCFAs)

SCFAs contain 1–6 carbon atoms. Acetate, propionate and butyrate produced in colon in ≈60:20:20 ratio, by bacterial fermentation of undigested carbohydrate. Combined concentration in large bowel 50–150mM. Act locally, and also absorbed. Important source of fuel for colonic mucosa so ↓ fibre intake with enteral feeding or diversion of faecal stream by ileostomy or colostomy can result in mucosal atrophy and ➲ diversion colitis. Also regulate food intake by ↑ satiety (↑ peptide YY and glucagon-like peptide-1 release) and exert local anti-inflammatory effects (↓ TNF-α, IL-6, and IL-12; ↓ NF-κB activation; ↑ Treg differentiation), which may explain some of putative benefits of pre- and probiotics in ➲ ulcerative colitis.

Sickle cell anaemia (SCA)

Linked with range of GI problems, often hepatobiliary, because of haemolysis and ischaemia, or recurrent transfusion.

Clinical features

- Chronic asymptomatic jaundice may relate to haemolysis or benign intrahepatic cholestasis.
- ▲ **Acute abdominal pain** ▲ due to range of causes (see Box 4.75). Splenomegaly may occur due to sequestration or ➲ portal hypertension, but splenic infarction and hyposplenism usually develop by adulthood. Higher risk of GI infection if hyposplenic.
- Hepatic sequestration crisis: sickling or sequestration within liver presents with severe RUQ pain, tender hepatomegaly, and jaundice.
- Acute hepatic ischaemia due to vascular occlusion.
- ➲ Gallstones (pigmented) in >30% of adults, with ↑ rates of ➲ cholecystitis, ➲ choledocholithiasis, and ➲ acute pancreatitis.
- ➲ Hepatitis B, ➲ hepatitis C, and ➲ HIV more frequent.
- Transfusion iron overload with recurrent transfusions causes secondary ➲ haemochromatosis.

Investigations

Diagnosis of SCA usually established in childhood. Specific investigations depend on clinical presentation. In those with jaundice, general rules apply (see ▶ Approach to recent-onset jaundice).

- FBC. Typical Hb 60–80g/l, reticulocytes 10–20%. Serum electrophoresis detects HbS. Marked ↓ Hb with abdominal pain may suggest sequestration crisis.
- LFTs. Bn may be massively ↑ (>600µg/L). A split bilirubin test will narrow differential diagnosis. AST/ALT usually <1,000U/L) unless hepatic ischaemia/infarction or acute hepatitis.
- US with Doppler or contrast-enhanced CT useful to exclude biliary obstruction, hepatic infarction, or vascular occlusion (e.g. ➲ Budd–Chiari syndrome, ➲ portal vein thrombosis).
- Iron studies may suggest overload (see ➲ haemochromatosis).
- ▷ Liver biopsy rarely necessary, but may show sinusoidal dilatation and sickling and/or fibrosis with cirrhosis.

Box 4.75 Causes of acute abdominal pain in SCA

- Hepatic sickling/sequestration.
- Splenic sickling/sequestration.
- ➲ Cholecystitis.
- ➲ Acute pancreatitis.
- Renal vein thrombosis.
- ➲ Budd–Chiari syndrome.
- Hepatic artery thrombosis/hepatic infarction.
- ➲ Portal vein thrombosis.
- ➲ Intestinal ischaemia/infarction.

Management

- Seek expert haematology input.
- Pain relief (most patients will have established protocols, often with → OPIATES).
- Acute sickling crisis or sequestration treated with exchange transfusion (aim to ↓ HbS to <30%) and IV fluids. Keep warm and well oxygenated, and treat precipitant to crisis (e.g. infection).
- Specific management depends on diagnosis (e.g. see ➲ hepatitis B, ➲ hepatitis C, ➲ haemochromatosis, ➲ gallstones, ➲ choledocholithiasis).

Sinusoidal obstruction syndrome (SOS)

- Previously known as veno-occlusive disease (VOD), sinusoidal obstruction syndrome (SOS) occurs due to obstruction of terminal hepatic venules and hepatic sinusoids.
- Occurs in 10–50% of patients following bone marrow transplant (BMT), usually within first 21d. Severe cases carry 90% mortality. Pathogenesis involves fibrosis and obliteration of terminal hepatic venules due to deposition of clotting factors, RBCs, and haemosiderin-laden macrophages.
- Other causes include chemotherapy, drugs (including azathioprine and 6-MP), ingestion of pyrrolizidine alkaloid toxins (bush tea), arsenic poisoning, and post-➲ liver transplantation.
- Presentation may be similar to acute ➲ Budd–Chiari syndrome, with jaundice, tender hepatomegaly, and ascites. ▲ **Acute liver failure** ▲ and multiorgan involvement may occur. Circulatory failure tends to precede liver dysfunction.
- LFTs often show ↑ ALT/AST (deranged LFTs >20d post-BMT also require consideration of ➲ graft-versus-host disease). Doppler US may show reversal of portal vein flow, but hepatic venous flow normal. Transjugular liver biopsy (with portal pressure measurements) may make diagnosis.
- Prophylaxis with LMWH and → URSODEOXYCHOLIC ACID recommended. However, treatment of SOS difficult and traditionally has been supportive. Defibrotide shows considerable promise: binds to vascular endothelial cells, enhancing factors that contribute to fibrinolysis and suppressing those promoting coagulation.

Sjögren's/sicca syndrome

Lymphocytic infiltration of salivary glands causes keratoconjunctivitis and dry mouth. Dysphagia in 75%, mostly due to oesophageal dysmotility, but also ↑ incidence of ➲ oesophageal rings/webs. Chronic atrophic gastritis can occur, as can ➲ acute and ➲ chronic pancreatitis (perhaps as association with ➲ autoimmune pancreatitis); exocrine pancreatic secretion often impaired. ➲ Primary biliary cholangitis and ➲ coeliac disease more common in patients with Sjögren's syndrome. Blood tests (in Sjögren's syndrome) often show positive rheumatoid factor, ANA, anti-Ro, and anti-La antibodies. Much of the management is symptomatic (e.g. artificial tears and saliva), with close attention required to dental care. Immunosuppressants or B cell immunomodulators (e.g. rituximab) employed if severe systemic disease.

Slimming diets

Increasing obesity in Western societies has been paralleled by the range of slimming diets (see also ► Approach to obesity). Traditional advice centres on low calorie intake (800–1500kcal/d) with 30–35% energy from fat, 50% carbohydrate, and 10–15% protein, although these figures are still debated.

- **Low-fat high-carbohydrate diets** (<30% energy from fat). Effective way of ↓ weight but relative effectiveness of unrestricted low-fat high-carbohydrate diet compared with low-fat energy-restricted diets unknown. Low-fat diets and modification of fatty acid composition ↓ risk of type 2 diabetes and coronary heart disease.
- **Fixed energy deficit diets** Involve dietician individually calculating energy requirements based on basal metabolic rates and adjusting for physical activity. Energy deficit of ~600kcal/d will induce weight loss of ≈0.5kg/wk.
- **Meal replacement** Involves controlled portion products (shakes, bars, soups, pastas) replacing 2 meals/d (and snacks), while allowing 1 regular meal of 'healthy' foods. Calorie intake ≈1,200–1,600kcal/d effective in trials, although evidence of real-life efficacy (when meal replacement products need to be purchased by user) lacking.
- **Very low calorie diets** Provide 450–800kcal/d and use formula foods to replace all meals and snacks. Induce rapid weight loss, but no evidence of long-term efficacy. ➲ Gallstones are an important complication of weight loss faster than 1–2kg/wk.
- **Low glycaemic index (GI) foods**. Low GI foods (wholegrain cereals, fruit, legumes) are more slowly absorbed than foods such as glucose or white bread, and have less acute effect on postprandial glucose and insulin levels, which has been proposed to ↓ hunger and ↑ satiety. Some evidence suggests that low GI foods ↑ HDL cholesterol, ↓ triglycerides, and ↓ insulin resistance. Have role as part of conventional energy-restricted diet.

- **High-protein low-carbohydrate diets** (e.g. Atkins and Dukan diets). Currently popular but possibly unhealthy. Severe carbohydrate restriction leads to dietary composition of 25% protein, 5% carbohydrate, and 70% fat, sharply contrasting with most dietary recommendations. Carbohydrate restriction leads to hepatic glycogenolysis and ketosis. This induces mild euphoria and loss of body water (which accounts for much of weight loss). Evidence for long-term efficacy lacking. British Dietetic Association. 🖱 http://www.bda.com/. has issued warnings about adoption of long-term diets of this type.

Solitary rectal ulcer syndrome

Rare (incidence 1/100,000, equal in ♂ and ♀, seen in all age groups) but also frequently misdiagnosed. Cardinal feature is isolated erythema or ulceration of part of rectum, usually anterior wall.

Pathogenesis

Prolapse of rectal mucosa (possibly occurring internally and therefore not visible or palpable) and paradoxical contraction of pelvic floor thought to be important, possibly leading to mucosal ischaemia. Direct trauma due to rectal digitation has been implicated, but many lesions are above reach of finger.

Clinical features

- Passage of blood and mucus PR with straining and feeling of incomplete evacuation.
- Evidence of rectal prolapse.
- Classic sigmoidoscopic is of a single ulcer on anterior rectal wall 5–10cm from anal verge, but polypoid lesion may be seen in 25% or isolated patch of hyperaemia in 20% (Plate 36).
- Histology shows distortion of glands with oedema and fibrosis of lamina propria. Muscularis mucosae thickened and muscle fibres extend up between crypts.

Investigations

Symptoms, sigmoidoscopic appearances, and histology most important. Endoanal US may show thickening of internal sphincter, and ▷ defaecography studies may show abnormal patterns of defaecation. Barium studies and anorectal physiology not helpful.

Treatment

- Topical treatments do not help.
- Fibre supplementation disappointing, especially if rectal prolapse.
- ➲ Biofeedback may help if paradoxical puborectalis contraction.
- Surgery has a minor role and should be reserved for those with intractable symptoms and good evidence of prolapse. Options include rectopexy and resection of prolapsing muscosa, or faecal diversion. Rectopexy is the procedure of choice for patients with rectal prolapse; helps ≈50% but ↑ symptoms in some.

Sphincter of Oddi dysfunction (SOD)

Definition and clinical features

Hypertension of biliary/pancreatic sphincter may cause episodic pancreaticobiliary-type pain. Subcategorized into 3 clinical groups:

- Type I. Biliary pain associated with LFTs >2× ULN on >1 occasion with dilated CBD (>10mm on US, or 12mm on ERCP).
- Type II. Biliary pain with 1 or 2 of the above.
- Type III. Biliary pain with normal investigations.

Investigation

- Dilated CBD may be seen on US, CT or MRCP (CBD normally <7mm in diameter, but may be up to 9mm post-➢ cholecystectomy and in extreme elderly, in absence of other pathology).
- LFTs may be elevated during attacks of pain, therefore important to review blood tests when patient symptomatic.
- ➢ ERCP and ➢ sphincter of Oddi manometry (SOM) previously gold standard for investigation. Baseline sphincter pressure >40mmHg, or sustained peaks >100mmHg, traditionally used to make diagnosis. However, not indicated in SOD type I (because of reliable response to treatment irrespective of manometry), and no role in SOD type III (in view of negative findings of EPISOD study). Most centres now debate role in SOD type II.
- ➢ Scintigraphy (e.g. HIDA scan) may show delayed biliary emptying.

Management

- Low threshold for considering cholecystectomy in patients with unexplained biliary pain.
- SOD type I should be treated with sphincterotomy.
- Sphincterotomy ± manometry may be considered in SOD type II.
- Avoid ERCP + sphincterotomy in SOD type III (risk of post-ERCP pancreatitis up to 20%). Focus care on holistic approach to functional pain, including addressing psychological factors
- Medical therapies for SOD type II/III include antispasmodics and tricyclic antidepressants.
- ERCP, sphincterotomy, and manometry should only be performed at specialist centres due to procedural difficulty and complication rates.

Spontaneous bacterial peritonitis (SBP)

Common bacterial infection in patients with cirrhosis and ascites. Prevalence in hospitalized patients ≈10%. Bacterial translocation, bacteraemia, and impaired antimicrobial activity of ascitic fluid contribute. Gram-negative bacilli (especially ➔ *E. coli*) cause 80%.

Clinical features

Majority present with fever and signs of sepsis, but few abdominal features. Abdominal pain, peritonitis, diarrhoea, and ileus can occur. Asymptomatic in 10%. Liver decompensation, with worsening ▲ **hepatic encephalopathy** ▲, and renal failure important associations.

Investigation

Diagnostic ascitic tap mandatory in all patients admitted to hospital with ascites, because of high rate of SBP (see ► Approach to ascites).

- Ascitic white count. Neutrophils >250/mm^3 strongly suggestive of SBP, unless other intra-abdominal source of infection.
- Ascitic protein <10g/L merits antibiotic prophylaxis.
- Microscopy and culture. 5–10 ml of fluid should be inoculated into blood culture bottles with media for aerobes and anaerobes (not just into specimen bottles). Despite this, 20–40% of presumed SBP (i.e. ↑ WCC) culture negative. Isolation of multiple organisms raises possibility of contamination or intra-abdominal source (e.g. ➲ diverticular perforation).
- Some patients have ascitic neutrophil count <250/ mm^3 but positive ascitic fluid culture. This is known as bacterascites.

Management

- Treat on finding ascitic neutrophils >250cells/mm^3, without waiting for microbiological confirmation. Give third-generation → CEPHALOSPORIN (e.g. cefotaxime 2g IV bd).
- Quinolones should not be considered in patients taking these drugs as prophylaxis against SBP.
- Continue antibiotic until clinical sepsis resolved. If concern sepsis may be ongoing, re-tap ascites; can discontinue antibiotics if neutrophils <250cells/mm^3 and other indicators of infection normalized.
- Infusion of human albumin (1.5g/kg at time of diagnosis and 1g/kg on d3) ↓ frequency of ➲ hepatorenal syndrome and ↑ survival.
- Resolution of infection in 75–90%, but hospital mortality remains 20–40%, predicted by degree of renal failure (see also ➲ hepatorenal syndrome) and largely due to hepatic decompensation.
- Antibiotic prophylaxis recommended in patients with previous SBP and ascitic protein <15g/L. Quinolone (e.g. norfloxacin 400mg od PO, ciprofloxacin 750mg weekly PO) ↓ risk of SBP over next year from 70% to 20%.
- Episode of SBP predicts 50% 2y mortality. Patients who recover should be considered for ➲ liver transplantation.

Steatorrhoea

See: ► Approach to malabsorption and steatorrhoea.

Still's disease

Autoinflammatory disease, classically presenting with triad of fevers, joint pain, and a characteristic "salmon pink" rash. Associated with extreme hyperferritinaemia. Adult Still's disease often has GI manifestations, including weight loss (75%), hepatomegaly (45%), deranged LFTs (75%), and abdominal pain (50%). Liver failure can be associated with aspirin/NSAID use.

Strongyloides

Strongyloides stercoralis is one of the most important intestinal nematode infections, infecting 30–100 million people worldwide, and underdiagnosed. Threadworm endemic in tropical areas but, because of autoinfection, may persist for decades following exposure.

Pathogenesis

Rhabditiform larvae are excreted in stool of infected individuals, which moult twice between developing into infective filariform larvae. Infect new host by penetrating skin, hence walking barefoot and work involving skin contact with soil are risk factors for infection (others include alcohol misuse, and HIV or HTLV-1 co-infection). Larvae migrate through bloodstream to alveoli, then up trachea and swallowed. Adult worms (3mm long) reside in duodenum/jejunum. Eggs may hatch in stool prior to defaecation and larvae penetrate bowel wall, circulate to lung, and mature into more adults, setting up cycle of autoinfection.

Clinical features

- **Acute** Associated with path of larval migration to small intestine. Petechial rash at site of skin penetration, which may be followed by intense pruritus and oedema. Migration through lungs can cause pneumonitis and tracheal irritation.
- **Chronic** Most intestinal infections re , but can cause abdominal discomfort, bloating, bulky loose stools, and malabsorption (similar to ➔ giardiasis). Up to 75% have ➔ eosinophilia or ⇄ IgE (hence consider diagnosis if present in returning travellers or migrant).
- **Hyperinfection syndrome** Heavy infestation, generally a result of immunosuppression (including steroid therapy). May cause pneumonitis, pulmonary haemorrhage, profuse diarrhoea, bowel wall thickening, GI ulceration, and ➔ protein-losing enteropathy. Can be fatal, so screen all those with potential exposure or unexplained eosinophilia (and treat if positive) before starting immunosuppression.
- **Disseminated infection** Penetration of large numbers of larvae through intestinal wall can be associated with bacterial (often Gram-negative) sepsis. Untreated, mortality approaches 100%.

Investigations

- FBC. ➔ Eosinophilia in 50%.
- HTLV-1 serology. Co-infection ↑ risk of acquisition, complications, and treatment failure.
- Stool microscopy may show larvae or eggs (but only 30% sensitive, and negative in early infection). Methods developed to ↑ sensitivity (up to 75%), but laboratory need to know clinical query if these are to be performed.
- Several serological tests available, including indirect immunofluorescent antibody test (IFAT) and ELISA. Neither perfect, and both can give false-positives in ascariasis, hydatidosis, and toxocariasis.[6] False-negatives in first 4–6wk.

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[6] Requena-Ménder A *et al.* (2013). *PLOS Negl Trop Dis* **7**: e2002.

- Endoscopy. Most common appearances are duodenal spasm, bleeding, mucosal oedema, and thickened duodenal folds. Histology can show subtotal villous atrophy, lymphocytic infiltrate, eggs, and larvae in submucosa.

Management

- Ivermectin 200μg/kg PO 2 doses on consecutive days or 2wk apart (🖱 Cochrane review).
- Alternatives are albendazole 400mg PO bd or thiabendazole 25mg/kg/d PO bd for 3d.
- Extend courses if hyperinfection or disseminated disease, until negative stool examination for 2wk.[7]
- No definitive test of cure, although post:pre-treatment antibody titre ratio <0.6, or ↓ in eosinophil count, are reasonable indicators.

Superior mesenteric artery syndrome

The superior mesenteric artery comes off aorta at a right angle and crosses over duodenum just to right of midline. Rarely, artery may obstruct duodenum as it crosses over. Anatomical abnormalities (congenital or acquired) can give rise to syndrome, but most common risk factor is significant weight loss (resulting in loss of mesenteric fat pad). An acute angle between SMA and aorta might be relevant, but only seems to happen in very thin patients.

Clinical features

Include epigastric fullness and bloating after meals, and bilious vomiting. May resolve when patient lying prone, in left lateral decubitus, or knee-to-chest position.

Investigation

- CT or MRI may reveal dilated stomach and duodenum with sharp cut-off to right of midline, and provide information on amount of intra-abdominal and retroperitoneal fat.
- Arteriography, performed at same time as barium contrast study, can aid diagnosis.

Treatment

Decompression, possibly surgical. Most commonly duodeno-jejunostomy.

❗ Pitfall.
Do not forget other causes of duodenal dilatation, including ➔ systemic sclerosis, ➔ diabetes, and distal duodenal strictures.

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[7] Mejia R & Nutman TB (2012). *Curr Opin Infect Dis* **25**: 458–63.

Systemic lupus erythematosus (SLE) and the GI tract

Clinical features

- Anorexia, nausea, and vomiting occur in 50% but may be due to disease or treatment. Mouth ulcers common and usually painless. ➲ Sjögren's syndrome and dry mouth in 20%.
- Oesophageal symptoms common, but do not correlate well with results of ➢ oesophageal manometry. In contrast with ➲ systemic sclerosis, lower oesophageal sphincter rarely involved.
- Risk of ➲ peptic ulceration ↑ by combined NSAID and steroid use. PPIs indicated for gastroprotection.
- Most dangerous manifestation of intestinal involvement is vasculitis (2% prevalence, mortality 50%; most common in territory of superior mesenteric artery, although classically small vessels involved). Can progress to ulceration, haemorrhage, perforation, and infarction.
- Although rare overall in SLE, causes of acute abdominal presentation include:
  - Vasculitis, especially if active disease elsewhere.
  - Intra-abdominal thrombosis, secondary to vasculitis or antiphospholipid syndrome (see ➲ portal vein thrombosis).
  - Increased incidence of inflammatory bowel disease, most often ➲ ulcerative colitis.
  - Intestinal pseudo-obstruction and acute pancreatitis should also be considered.
- ➲ Protein-losing enteropathy and fat malabsorption can occur.
- Bear therapeutic immunosuppression in mind: thoroughly assess for bacterial, viral and fungal infections in appropriate clinical context.

Investigation

- Check inflammatory markers. ESR often disproportionately ↑ compared to CRP in active SLE, so if both elevated perform thorough search for infection. ↑ Anti-dsDNA, and ↓ complement components C3 & C4 also suggest active disease.
- Look for thumb-printing on plain AXR (suggests ischaemic bowel).
- CT can show abscesses, lymphadenopathy, serositis, bowel wall thickening, pancreatic pathology, and hepatosplenomegaly.
- Visceral angiography does not usually help, but colonoscopy with biopsy can diagnose vasculitis.

Management

Treatment of vasculitis with IV pulsed steroids can be effective, but vital to exclude infection (e.g. with stool and blood cultures) beforehand. Complex nutritional support may be required while treatment undertaken. Seek expert rheumatology input.

Systemic mastocytosis

Rare disorder resulting from excessive histamine and prostacyclin release from inappropriate mast cell proliferation in skin, bones, lymph nodes, and spleen. Classic skin sign is multiple red-brown papules (urticaria pigmentosa). 80% have GI symptoms of nausea, vomiting, diarrhoea, or abdominal pain. May present with steatorrhoea (see ► Approach to malabsorption and steatorrhoea). Symptoms often brought on by alcohol. May develop hepatosplenomegaly and portal hypertension. Serum tryptase useful as initial screen, but diagnosis made by demonstrating multifocal infiltrates of mast cells in biopsies of extracutaneous organs ± bone marrow. Treatment symptomatic with antihistamines, mast cell stabilizers (sodium cromoglycate), → PROTON PUMP INHIBITORS ± → CORTICOSTEROIDS. Long-term risk of transformation to mast cell leukaemia.

Systemic sclerosis and the GI tract

(see Plate 2)

Connective tissue proliferation with fibrosis results in GI manifestations in 80% of systemic sclerosis patients, often with >1 site affected. Treatment symptomatic and supportive only, and often very difficult.

- **Oesophagus** Abnormal peristalsis results in ➲ gastro-oesophageal reflux disease (GORD), intermittent dysphagia, and often stricturing. ⮚ Oesophageal manometry shows lack of propagated swallows and low-amplitude contractions. High-dose → PROTON PUMP INHIBITORS needed to control reflux. Prokinetics theoretically ↑ lower oesophageal sphincter tone and speed gastric emptying, but may not work.
- **Stomach** ↓ gastric emptying common and aggravates GORD. Prokinetics should be tried. Erythromycin is a motilin agonist and can speed gastric emptying. If intractable early satiety, low-volume overnight PEG feeding can be very helpful. One useful manoeuvre is to place jejunal extension through the PEG. Bleeding from telangiectasia managed as described in ► Approach to anaemia and occult GI bleeding.
- **Small bowel** Reduced motility, ➲ jejunal diverticulae, and consequent ➲ bacterial overgrowth may cause bloating, cramps, or signs of malabsorption. Barium studies useful (follow-through shows 'stacked coin' appearance). Bacterial overgrowth can be treated with low-dose antibiotics (tetracycline 250mg bd or metronidazole 400mg bd for 10d). Bacterial culture and sensitivities rarely useful. Prokinetics can be tried. ➲ Pseudo-obstruction sometimes seen and in worst cases ➲ parenteral nutrition needed. Malabsorption may be aggravated by ➲ pancreatic insufficiency (exocrine output ↓ in 30%).
- **Large bowel** Colon may be atonic, and severe constipation is common. In our experience, non-stimulant osmotic laxatives (e.g. macrogols) are the best agents to help this. Thinning and fibrosis of anal sphincters common and may explain ↑ incidence of passive faecal incontinence.

Section 4

T

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Tapeworms (cestodes)

Intestinal cestodes do not usually produce severe clinical signs. Many are unaware they are infected until they pass tapeworm segments. Heavy infestations can cause abdominal pain, anorexia, nausea, diarrhoea, and weight loss.

Fish-borne tapeworms

Diphyllobothrium latum acquired by eating raw or undercooked freshwater fish. Endemic in Europe, Russia, and Alaska. Worm is not invasive, and most cases are not aware they are parasitized until expel tapeworm naturally. Absorbs nutrients, including ➔ vitamin B_{12}, and can cause deficiency. Diagnosis by finding eggs in stool. Treatment: praziquantel (single dose 10mg/kg) or albendazole 400mg/d for 3d.

Meat-borne tapeworms

Colonization occurs by eating raw or undercooked meat containing cysticerci of *Taenia saginata* (beef), *Taenia solium* (pig), or *Taenia asiatica* (pigs and cattle). Endemic in Latin America, India, SE Asia, and Africa. Readily preventable with public health measures.

Clinical features

Most infections are asymptomatic. Most feared complication is neurocysticercosis, which occurs with *T. solium*. Release oncospheres that penetrate intestinal wall and migrate to brain, spinal cord, meninges, eye, and heart. Can have long latent phase. Major manifestation is seizures, though can produce variety of neurology (focal signs in 16%, ↑ intracranial pressure in 12%, and cognitive decline in 5%).

Diagnosis

- **Intestinal taeniasis** Stool microscopy for eggs or proglottids. Sensitivity improved by combining with ELISA. Often cleared by time neurology symptoms develop.
- **Neurocysticercosis** Neuroimaging, confirmed by serology:
  - CT or MRI show nodular or cystic lesions, depending on stage.
  - Serum antibodies positive in 98% of patents with >1 viable cyst or subarachnoid disease, but only 50–60% in patients with one intracranial cysticercus (therefore negative test cannot exclude). Antibodies frequently reported in asymptomatic individuals in endemic regions.
  - CSF often abnormal but non-specific, with mononuclear pleocytosis and mild ↑ protein. CSF antibody/PCR assays variable.

Treatment

- **Intestinal taeniasis** Praziquantel 25mg/kg, single dose, or albendazole 400mg/d for 3d.
- **Neurocysticercosis** Get specialist advice. Therapeutic approaches include symptomatic therapy (e.g. anticonvulsants), antiparasitic drugs (albendazole 15mg/kg/d or praziquantel 50mg/kg/d for 2wk + steroid cover), or surgery (lesion resection or shunt placement).[1]

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[1] Garcia HH *et al.* (2014). *Lancet Neurol* **13**: 1202–15.

Other tapeworms

For echinococcus infections, see ➲ hydatid disease. Minority of other infections can occur. *Mesocestoides lineatus* and *Spirometra erinacei* acquired from eating 'backyard-reared' chickens, snails, snakes, or frogs. Dwarf tapeworm (*Hymenolepis nana*) transmitted person-to-person; may cause severe disease in immunocompromised.[2]

Telangiectasia

See: ➲ Hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu syndrome).

TIPSS (transjugular intrahepatic portosystemic shunt)

Technique

- Involves formation of an artificial tract through the liver between the portal and hepatic veins, using a radiologically placed metal stent (Fig. 4.21).
- Used in treatment of complications of ➲ portal hypertension. Aims to ↓ hepatic venous pressure gradient (HVPG) to <12mmHg.
- Performed in specialist liver units. Does not preclude ➲ liver transplantation.

Indications

- Uncontrolled variceal bleeding (see ▲ **Acute upper GI bleeding** ▲), where drug and endoscopic therapy have failed, is the main indication. ➲ Sengstaken–Blakemore tube may be inserted prior to TIPSS. Especially useful for gastric and ectopic (e.g. rectal) varices.
- Early use after variceal bleed in cirrhotic patients at high risk of re-bleed improves long-term survival compared with standard secondary prevention with β-blockers and endoscopic variceal eradication.[3]
- Refractory ascites (see ▷ Approach to ascites). Reduces need for large volume ▷ paracentesis, but no comparative ↓ mortality, and ↑ risk of ▲ **hepatic encephalopathy** ▲.
- Efficacy reported in ➲ Budd–Chiari syndrome, type 1 and 2 ➲ hepatorenal syndrome, ➲ sinusoidal obstructive syndrome, hepatic hydrothorax, ➲ hepatopulmonary syndrome, ➲ portal vein thrombosis, ➲ sinusoidal obstruction syndrome, and portal hypertensive gastropathy, but few controlled studies.
- Patients aged >70y or with MELD >15 have poorer outcomes.

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[2] Ito A & Budke CM (2014). *Travel Med Infect Dis* **12**: 582–91.

[3] Afdhal NH & Curry MP (2010). *N Engl J Med* **362**: 2421–2.

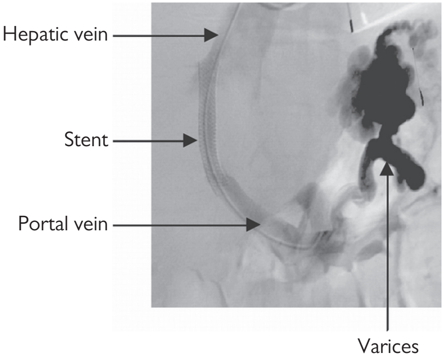

Fig. 4.21 Transjugular intrahepatic portosystemic shunt (TIPSS).

Absolute contraindications

- Intrahepatic lesions (e.g. cysts, tumours).
- Vascular obstruction (complete hepatic/➲ portal vein thrombosis).
- Cardiopulmonary disease (severe pulmonary hypertension, congestive cardiac failure, severe tricuspid regurgitation).
- Progressive renal failure.
- Primary prevention of variceal bleeding.
- Uncontrolled sepsis.

Relative contraindications

- Severe coagulopathy (INR >3, platelets $<20 \times 10^9$/L).
- Biliary obstruction (risk of biliary puncture/fistula).
- ▲ **Hepatic encephalopathy** ▲.
- Moderate pulmonary hypertension.

Complications

- Direct procedure-related mortality 0–2%, and 30d mortality 7–45%, depending on indication.
- TIPSS blockage. Early thrombosis in 10–15%, but dysfunction in 80% by 1y (thrombosis or intimal hyperplasia). Covered stents may ↓ dysfunction. Blockage clinically suggested by further portal hypertensive complications. Doppler US within 1wk of insertion, and formal venography at 1y, suggested to exclude occlusion.
- New/worsened ▲ **hepatic encephalopathy** ▲ in 10–44% limits use (particularly in ➲ Child–Pugh C disease). May necessitate stent diameter reduction or occlusion.
- Direct procedure-related complications (e.g. ➲ haemobilia, intraperitoneal bleed, hepatic infarction, arteriovenous fistulae, sepsis) in <15%, but major complication in <3%.
- Haemolysis due to flow through shunt in 10–15%, but usually resolves in <4wk.

TNM classification

Initially devised by Pierre Denoix in 1943, and widely used for staging solid tumours. Provides prognostic information and guides management. Developed and maintained by Union for International Cancer Control to provide globally recognized system for classifying extent and spread of malignancy. **T** describes size of primary tumour and invasion of adjacent tissues (Tx: cannot be evaluated; Tis: carcinoma *in situ*); **N** indicates regional lymph node involvement; and **M** presence of distant metastases. Does not apply to haematological malignancies, ovarian cancer, or brain tumours. Specific scoring varies between different tumour types, so see individual entries under ➲ oesophageal cancer, ➲ gastric cancer, ➲ colon cancer and ➲ rectal cancer ➲ colorectal cancer (but see also ➲ Dukes classification), ➲ hepatocellular carcinoma, ➲ pancreatic cancer, and ➲ cholangiocarcinoma.

Toxic megacolon

- Life-threatening complication of inflammatory bowel disease or infective colitis. Characterized by segmental or generalized colonic dilatation (without obstruction) + systemic features of toxicity.
- Toxic features include: fever, tachycardia, hypotension, volume depletion, mental status change, ↑ WBC, anaemia, and electrolyte abnormalities (Jalan criteria).
- Colonic dilatation defined as transverse colonic diameter >6cm with loss of haustration (➲ megacolon). Incidence ↓ due to improvements in medical care for severe colitis but can occur in up to 5%, and can be triggered by opiates or hypokalaemia.
- Clinical suspicion should trigger abdominal imaging. AXR often adequate to demonstrate massively dilated colon although CT used to exclude perforation.

Treatment

- Management should be directed by MDT including a gastroenterologist and surgeon. Patients require frequent assessment.
- Patients should be NBM, receive adequate IV fluid resuscitation, and have electrolyte abnormalities corrected.
- Medication should be reviewed to cease any that could worsen condition (e.g. anticholinergics, opioids).
- Underlying cause should be treated, including antibiotics for infective causes and IV steroids for inflammatory bowel disease.
- Deterioration or failure of medical management mandate surgery.
- Endoscopic decompression not recommended. However, can attempt 'rolling techniques'. Air accumulates in transverse colon because it is most the anterior portion of the colon, and rolling patient into prone position for 15min every 2h can assist decompression.

Prognosis

50% respond to medical therapy. Prognosis worse if surgery required.

TPMT (thiopurine methyltransferase)

- TPMT plays key role in the metabolic pathway of → AZATHIOPRINE/ → 6-MERCAPTOPURINE (6-MP) (see Fig. 4.22). Variations in TPMT (largely determined genetically) allow shunting of 6-MP into 6-methylmercaptopurine (6-MMP) when levels are normal or high. Normal range: 25–55nmol/g.
- Patients homozygous for recessive polymorphisms resulting in inactivation of TPMT (1/300) produce very high levels of 6-thioguanine nucleotides (TGN) that make them unlikely to tolerate thiopurines at all (with high risk of side-effects such as significant neutropaenia).
- People heterozygous for TPMT polymorphism (10% of population) require lower doses of thiopurines.
- Important to recognize that TPMT accounts for some but not all of azathioprine/6-MP toxicity.
- High metabolizers (>55nmol/g) may catabolize intermediaries so rapidly they have minimal therapeutic effect. Higher doses or alternative agents may be necessary.
- Direct measurement of TGN and 6-MMP allow further refinement of prediction of toxicity and therapeutic response (see also ⊳ therapeutic drug monitoring in IBD, p. 150). Desired metabolite profile favours 6-TGN production over 6-MMP. ~15%, of patients with inflammatory bowel disease preferentially metabolize thiopurines toward 6-MMP. Allopurinol, a xanthine oxidase inhibitor, can switch metabolism toward 6-TGN, and is ∴ used in these patients.

TPN

See: ➔ Parenteral nutrition.

Tracheo-oesophageal fistula (TOF)

Background

- Congenital cause:
  - Trachea communicates with abnormal atretic distal oesophagus (due to failure of lung bud to separate from foregut).
- Acquired causes:
  - Tumour invasion (e.g. bronchial or ➔ oesophageal tumour)
  - Instrumentation (e.g. ⊳ endoscopic dilatation or treatment of malignant stricture).

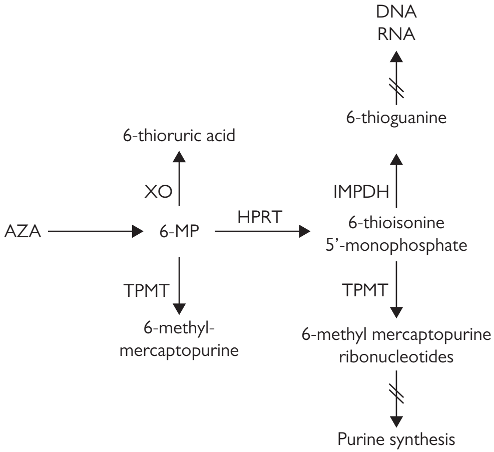
DNA
RNA
6-thioguanine
6-thioruric acid
XO
IMPDH
AZA
6-MP
HPRT
6-thioisonine
5'-monophosphate
TPMT
TPMT
6-methyl-
mercaptopurine
6-methyl mercaptopurine
ribonucleotides
Purine synthesis

Fig. 4.22 Metabolism of → azathioprine/➔ 6-mercaptopurine. Azathioprine converted to 6-MP non-enzymatically: AZA, azathioprine; 6-MP, 6-mercaptopurine; XO, xanthine oxidase; HPRT, hypoxanthine phosphoribosyltransferase; TPMT, thiopurine methyltransferase; IMPDH, inosine monophosphate dehydrogenase.

Clinical features

- Congenital TOF usually presents following birth or in infancy with regurgitation and aspiration of feed (due to associated atresia as well as TOF). Associated developmental abnormalities common.
- In adulthood, TOF presents with features of ▲ **oesophageal rupture** ▲, recurrent pneumonia, and systemic sepsis.

Investigation

- Congenital TOF diagnosed with prenatal US in context of lower than expected weight. Abnormalities of stomach confirmed by failure to pass NG tube, and rarely with injection of 1ml Gastrografin® down tube.
- CXR may show air-filled upper oesophagus and air–fluid level.
- In adulthood, CT may show fistula, with diagnosis confirmed using oral non-ionic contrast, if necessary.

Management

- Congenital TOF treated surgically with resection of oesophageal atresia and TOF, and end-to-end anastomosis or interposition of colon, depending on length of defect. Surgery 90% successful, but may cause significant reflux and oesophageal motility problems in adulthood.
- Endoscopically placed covered metal stents may be effective in sealing defect in >70% of cases of TOFs related to oesophageal cancers. Other techniques for closure include endoscopic clips, glue, or suturing devices.

Traveller's diarrhoea

See: ► Approach to acute diarrhoea.

Trematodes

See: ➲ Flukes (flatworms, trematodes).

Tropical pancreatitis

In tropical developing countries there is distinct non-alcoholic type of chronic pancreatitis of uncertain aetiology that is more common than alcoholic pancreatitis. Proposed causes are malnutrition, dietary toxins (e.g. cassava) and genetic factors (*SPINK* gene).

Clinical features

Patients often young, presenting in 2nd-3rd decades. 70% ♂. Often have aggressive diabetes, large pancreatic calculi in large ducts with marked ductal dilatation, and accelerated course of disease. Prevalence of pancreatic cancer higher than with other causes of pancreatitis.

Investigations and management

As for ➲ chronic pancreatitis. Insulin usually required early for diabetes with monitoring for microvascular complications, as this is the usual cause of mortality in these patients.

Tropical sprue

Initially described by Hilary in 1759, who wrote observations of chronic diarrhoea in Barbados. Characterized by chronic diarrhoea and malabsorption in residents or visitors to tropics. Defined as 'malabsorption of at least two different substances in people in tropics when other causes have been excluded'.

Epidemiology

Restricted to SE Asia, Caribbean, and Central South America. Usually occurs in long-term visitors or residents of >6mo, but epidemics have occurred in India and Burma. Prevalence may be falling due to increasing self-medication with antibiotics.

Clinical features

- Chronic diarrhoea with steatorrhoea, anorexia, cramps, and bloating. May be ➲ lactose intolerance, vitamin B_{12} or vitamin A deficiency, hypocalcaemia, anaemia, stomatitis, glossitis, and oedema.
- Pathological features include atrophic gastritis (though this may relate to co-infection with *Helicobacter*) and mild changes in colonic epithelial cells, but major changes are in small intestine. There is ↓ disaccharidase activity and fat absorption: latter may account in part for altered transit time through small bowel. Aetiology still uncertain but likely to involve chronic infection with enteropathogens.

Diagnosis

Requires demonstration of partial villous atrophy, exclusion of specific cause of diarrhoea and malabsorption, and presence of fat and B_{12} malabsorption.

- Search carefully for intestinal pathogens. Three stool specimens for microscopy, with particular attention to looking for ➲ microsporidia and *Isospora* in immunocompromised.
- Duodenal biopsy or serology may be helpful for diagnosing ➲ giardiasis and ➲ *Strongyloides* (faecal microscopy insensitive).
- ➲ Coeliac serology important to exclude gluten-sensitive disease.
- Contrast examination or capsule endoscopy of small bowel may be needed to exclude ➲ lymphoma.

Treatment

- 'Simple' general measures (restoring water and electrolytes, replacing nutritional deficiencies of iron, folate, B_{12}) ↓ mortality of epidemic sprue.
- Use of antibiotics controversial, but overland travellers improve on tetracycline 250mg PO qds, usually given for several months, or combination antibiotics in persistent cases for up to 1y.

Prognosis

Good, particularly in expatriates returning from tropics. Some evidence of recurrence in indigenous populations of the tropics.

Trypanosomiasis

Trypanosoma cruzi is endemic in central Brazil, Venezuela, and Argentina, and spread between humans by reduviid bugs of the *Triatominae* group. The name 'reduviid' comes from the Latin *reduvia*, meaning hangnail, and relates to their curved powerful beaks adapted to suck blood from mammals. Bugs defaecate when biting, and parasite introduced when the bite is scratched. Chronic disease results from widespread destruction of autonomic ganglion cells in heart, gut, respiratory tract, and urinary tract.

Acute phase associated with high number of parasites, but tends to be mild with a skin lesion and constitutional symptoms. In chronic phase, parasites found within end organs. Autoimmune damage thought to occur via cardiac or nerve epitopes cross-reacting with *T. cruzi* antigens.

Clinical features

- GI involvement can produce megaduodenum or ➲ megacolon, as well as megaoesophagus, which helps distinguish from idiopathic ➲ achalasia. Small bowel dilatation and lack of peristalsis can also be found.
- Cardiac arrhythmias can be fatal.

Diagnosis

Can be made by demonstration of trypanosome forms on blood smears, but more usually by serological complement fixation test.

Treatment

- Treatment of the infection in acute, early chronic, and relapsed immunosuppressed patient uses nifurtimox and benznidazole.
- Treatment of achalasia syndrome in Chagas' disease similar to idiopathic ➲ achalasia.

Tuberculosis and the GI tract

Abdominal tuberculosis (TB) can manifest in four ways: tubercular lymphadenopathy, peritoneal disease, gastrointestinal TB, and visceral involvement.

Tubercular lymphadenopathy

Most common presentation. Usually follows drainage pattern of affected organ, although can also arise from haematogenous or contiguous spread. Imaging non-specific; most common appearance is multiple mildly enlarged nodes in clusters, but can vary from ↑ in number of normal-sized nodes to formation of conglomerate nodal masses. Nodes usually have central areas of caseous necrosis with peripheral enhancement.

Peritoneal tuberculosis

Manifestations may include:

- Ascites. Suggestive features include mononuclear pleocytosis, protein concentration >30g/L, SAAG <11, and low glucose. Yield of organisms on microscopy <5% and culture <20%. Associated peritoneal enhancement usually present. See also ➢ Approach to ascites.
- Fibrosis. Characterized by omental and mesenteric involvement, and presence of matted bowel loops. Loculated ascites sometimes present.
- Peritoneal reaction. Presents with nodules and adhesions.

Gastrointestinal tuberculosis

Historically related to severity of pulmonary involvement, especially cavitation and positive sputum smears (↑ risk of swallowing organisms). In modern series, CXR unremarkable in most patients. Incidence has risen, partly due to prevalence of HIV infection, and partly due to more extensive use of anti-TNF agents.

Location and pathology

Ileocaecal area and jejunum most commonly affected. Has ulcerative, inflammatory, and stricturing phenotypes. Incompetence of ileocaecal valve (due to disease on either side) said to distinguish TB from ➲ Crohn's disease. Key pathological features are thickening of bowel wall, transmural granulomas (caseation often seen in regional lymph nodes but not always in mucosal granulomata), mesenteric adenopathy, and serosal tubercles easily visible on laparotomy/laparoscopy but not on CT.

Clinical features

Abdominal pain (90%), weight loss, fever, altered bowel habit. Two-thirds have RIF mass. Complications: bowel obstruction, perforation.

Diagnosis

- Often delayed and difficult. Differential includes ➔ Crohn's disease, ➔ *Yersinia*, caecal malignancy, ➔ actinomycosis, and ➔ amoebiasis. Syphilis and lymphogranuloma venereum often quoted but extremely rare.
- Endoscopic biopsy. Acid-fast bacilli seen in minority. Organism can be cultured from infected tissues but takes 6–12wk. PCR assays substantially ↓ diagnostic wait times.
- Immunological assays:
  - Tuberculin skin test. Insufficiently reliable. Positive result does not always indicate active disease and, where immune response impaired (e.g. elderly, HIV co-infection), can be false negative.
  - Interferon-γ release assays (IGRAs, e.g. QuantiFERON-Gold) have similar limitations (sensitivity ≈80%, specificity 85%).[4]
- Laparoscopy can be useful in allowing biopsy of serosal nodules.

Visceral tuberculosis

Involvement of abdominal solid organs occurs in ≈20% of patients with abdominal TB. Genitourinary system most commonly affected, followed by liver (see ➔ hepatic granulomas), spleen and pancreas (can mimic pancreatitis or tumour). Mode of spread: haematogenous. May be asymptomatic, or present with non-specific symptoms. Diagnosis may be suggested by serological testing and imaging, but definitive diagnosis requires biopsy with histology with staining for AFB, and culture ± molecular techniques for mycobacterial detection.

Treatment

No controlled studies, but standard treatment is conventional chemotherapy (rifampicin, isoniazid, pyrazinamide, ethambutol) for 2mo then rifampicin + isoniazid for further 4–8mo. In HIV co-infection where CD4 count <100 × 10^6/L, concomitant HAART recommended.

Tumour staging

See: ➔ TNM classification, or entries on individual cancer subtypes.

Turcot's syndrome

Characterized by familial colonic polyposis and primary tumours of CNS. Autosomal dominant. Most common group has germline mutation in *APC*, similar to ➔ familial adenomatous polyposis, and the CNS tumours tend to be medulloblastomas. Second group has germline mutations in mismatch repair genes typical of Lynch syndrome and associated with glioblastoma multiforme. Associated genes are *MLH1* and *PMS2*. Colonic screening guidelines similar to those for individuals with FAP or Lynch syndrome.

---

[4] Ng SC *et al.* (2014). *J Gastroenterol Hepatol* **29**: 1664–70.

Tylosis

Autosomal dominant disease characterized by hyperkeratosis of palms and soles of feet. High incidence of oesophageal, bronchial, and laryngeal cancer, often at younger age than usual (oesophageal cancer in >90% of cases by 65y; see ➔ oesophageal tumours). Endoscopic surveillance suggested from age 30, repeating every 1–3y.

Typhlitis

Background

- From Greek *typhlon*, meaning caecum, but also known as ileocaecal syndrome and neutropaenic enterocolitis.
- Occurs almost exclusively in immunocompromised, neutropaenic patients (e.g. HIV, post-bone marrow transplant).
- Characterized by transmural inflammation of caecum, although ascending colon and ileum can be involved as well.
- Rarely diagnosed by gastroenterologists, but accounts for 10% of deaths in children with leukaemia during chemotherapy.
- Aetiology unknown, but important factors may include mucosal injury due to cytotoxics, ➔ cytomegalovirus, bacterial infection, and mucosal ischaemia. ➔ *Pseudomonas* has been implicated.

Clinical features

Suspect in neutropaenic patient with following symptoms and signs:

- Nausea, vomiting, fever.
- Generalized or right-sided abdominal pain + tenderness.
- Diarrhoea (and blood).
- Shock due to secondary sepsis or caecal perforation.

Investigations

- Important to exclude other causes (e.g. ➔ *C. difficile*).
- Neutrophil count almost always $<0.1 \times 10^9$/L.
- AXR may show free air (perforation) or ‘thumb-printing’, but can be featureless.
- US or CT may show caecal distension; caecal, right colon, or terminal ileum wall thickening (>3 mm); and perforation.
- Bowel wall thickness associated with prognosis: >10mm associated with 60% mortality.
- Endoscopic examination relatively contraindicated and almost always unnecessary.

Management

- NBM, NG tube, and gastric decompression.
- IV fluid and electrolyte replacement.
- Broad-spectrum antibiotics (e.g. 3rd-generation → CEPHALOSPORIN + → METRONIDAZOLE) initially, with therapy then tailored according to blood culture results.
- Review medication to cease any that can worsen condition (e.g. anticholinergics, opioids).
- Recovery often slow. Most patients require TPN.
- Surgery necessary for perforation (and some advocate at diagnosis in view of 40–50% mortality associated with caecal perforation, bowel necrosis, and sepsis).

Prognosis

Poor. Mortality ≈40–50%.

Section 4

U

Ulcerative colitis *578*

Ulcerative colitis

Inflammatory condition that affects rectum and extends proximally to involve variable amount of colon. First differentiated from infectious colitis in 1859 by Samuel Wilks.

Epidemiology

Found worldwide but incidence varies ~10-fold between areas of high incidence (UK, USA, Northern Europe, Australia: incidence ~20/100,000/y; prevalence ~100/100,000 population) and low incidence (Asia, Japan, South America). Similar to ➔ Crohn's disease, incidence has ↑ over the last 50 years.[1] Affects ♂ and ♀ equally. Peak onset age 20–40y, but 2nd smaller peak in older adults. Said to affect Ashkenazi Jews more frequently, but lower incidence among Jews in Israel compared with those in USA suggests environmental factors play a role.

Aetiology

Unproven. Hypotheses include infection, immune response to bacteria or self-antigens, role of nervous system ('stress'), and possible abnormalities in colonic epithelial cells or mucosal permeability. Few explain the predominantly left-sided nature of the disease.

- **Infection** No specific pathogen identified. There may be differences in adhesion of *E. coli* from patients compared with controls. There is also evidence of gut microbiome dysbiosis, but significance debated.
- **Immunopathogenesis** Increased IgG1 and IgG3 secreting plasma cells, autoantibodies to epithelial cell components, and p-ANCA (60–80% patients) have been demonstrated. Changes in T cells and intraepithelial lymphocytes inconsistent and of uncertain relevance. There is strong epithelial expression of MHC class II antigens in active colitis, which may alter antigen expression to local T cells. Many changes in immune function may be secondary to increased levels of pro-inflammatory cytokines (IL-1, IL-6, interferon-γ). New data also suggest inflammation resolution may be abnormal in UC.
- **Genetics** Disease concordance rates 13% for monozygotic and 2% for dizygotic twins, more than allowable by chance but less than occurs in ➔ Crohn's disease. Recently, Genome-Wide Association Studies (GWAS) have identified 163 IBD susceptibility loci, of which 110 shared between UC and CD. How these contribute to pathogenesis currently unclear, and in fact the polymorphisms identified to date account for only 7.5% of UC heritability.

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[1] Molodecky NA *et al.* (2012). *Gastroenterology* **142**: 46–54.

Clinical features

Symptoms Bloody diarrhoea, and mucus per rectum. Urgency of defaecation and tenesmus are common. Abdominal discomfort occurs but pain usually not as prominent as in ➔ Crohn's disease. Symptoms do not always correlate with endoscopic severity. Onset typically slow and insidious, but acute onset can occur and UC can be precipitated by an acute infectious colitis. Blood and pus are usually mixed in with stool, but pure blood alone may be seen in disease localized to rectum (proctitis). Although most patients with active disease have diarrhoea, those with proctitis may complain of constipation or hard stools. Systemic symptoms are common in severe attacks, where there may be anorexia, vomiting, fever, and symptoms of anaemia.

Signs Affected bowel may be tender on abdominal examination, but bowel sounds usually normal unless colon very dilated. Signs of dehydration, fever, weight loss, and tachycardia are evidence of acute severe colitis. There may be extraintestinal manifestations (Box 4.76).

Assessing disease severity: Although there are endoscopic and histological scoring systems, the clinical criteria of Truelove and Witts[2] are still used as a guide to decide on admission and IV therapy.

- Mild: <4 bloody stools per day, no systemic disturbance.
- Moderat**e**: 4–6 bloody stools/day, minimal systemic disturbance.
- Severe: >6 bloody stools per day, with systemic disturbance (fever, tachycardia, anaemia, or ESR/CRP >30).

Laboratory markers of severity: ↑ CRP, ↑ platelets, ↓ albumin, ↓ Hb.

Pathology 50% have disease confined to sigmoid or rectum, 30% have disease beyond sigmoid but not affecting the whole colon, and 20% have pancolitis. Rectal sparing can be seen as a result of topical treatment with steroids or 5-ASA. Although shortening and narrowing of colon can occur as a result of chronic disease, fibrosis and stricturing are uncommon. Microscopic features: inflammation confined to the mucosa, with neutrophils, lymphocytes, macrophages, and eosinophil infiltrating. There is crypt distortion, goblet cell depletion, Paneth cell metaplasia, and basal plasmacytosis.

Extraintestinal manifestations (Box 4.76) ❗ Important association between UC and thromboembolism (DVT and PE) in severe disease. Hospitalization, immobility, and malnutrition contribute, but in addition platelets can be high and many clotting factors are increased. Patients with severe disease should receive prophylactic anticoagulation despite lower GI bleeding.

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[2] Truelove SC, Witts LJ (1995). *BMJ* **ii**: 1041.

Box 4.76 Extraintestinal manifestations of UC

Related to activity of colitis

- Peripheral arthropathy.
- ➔ Erythema nodosum.
- Episcleritis.
- Aphthous (mouth) ulcers.

Usually related to activity of colitis

- ➔ Pyoderma gangrenosum.
- Anterior uveitis.

Unrelated to colitis

- Sacroiliitis.
- Ankylosing spondylitis.
- ➔ Primary sclerosing cholangitis.

Rare

- Pericarditis.
- ➔ Amyloidosis.

Diagnosis and differential diagnosis

Rests on the clinical picture, especially history, endoscopic appearances, and histology of colonic biopsy specimens, alongside microbiological exclusion of infectious colitis (see Box 4.77). Endoscopic appearances vary with severity of disease from mild (oedema, loss of vascularity, and patchy subepithelial haemorrhage) to severe (loss of vascular pattern, haemorrhage, mucopus, ulceration, and loss of epithelium, sometimes with small islands of residual mucosa that can be mistaken for polyps and therefore are called 'pseudo-polyps') (Plate 22).

Box 4.77 Histological differentiation of infective from UC

Difficult, but the following features suggest chronicity and help to make diagnosis with probability >80%:

- Distorted crypt architecture.
- Crypt atrophy.
- Irregular mucosal surface.
- Basal lymphoid aggregates.
- Chronic inflammatory infiltrate.
- Goblet cell depletion.

Always consider ➔ Crohn's colitis in differential diagnosis: ileoscopy or radiological small bowel evaluation often necessary (especially if inflammation appears confined to rectum but inflammatory markers raised, low albumin, or anaemia). Exclude infectious colitis and other forms of segmental colitis such as ischaemia, ➔ radiation colitis, ➔ microscopic colitis, and drug-induced colitis (culprits include NSAIDs, antibiotics, and ➔ immune checkpoint inhibitor induced enterocolitis).

Investigations

- **Blood tests** Check for anaemia and iron deficiency. Thrombocytosis, eosinophilia, and leukocytosis may all reflect active disease. Hypokalaemia, hypoalbuminaemia, and abnormal LFTs may be associated with severe disease or ➲ primary sclerosing cholangitis.
- **Stool tests** Always send stool for C. *difficile* toxin, as well as microscopy and culture. Faecal calprotectin and lactoferrin are markers of neutrophils in faeces, and increase with active inflammation. Can be used to aid differentiation of IBD from ➲ irritable bowel syndrome. Increasingly used in monitoring efficacy of medical therapy (to avoid need for colonoscopy). See also ➤ CPD, p. 151.
- **Endoscopy** Colonoscopy usually not necessary for diagnosis (sigmoidoscopy often sufficient) but can help determine disease extent. See ➲ Mayo score for guidance on severity grading. Although colonoscopy is safe in expert hands, cannot be recommended for general use in severe disease. Limited flexible sigmoidoscopy and biopsy for CMV histology should be considered in refractory or severe disease, particularly in patients who deteriorate soon after up-titration of immunosuppression. In assessment of chronic colitis and dysplasia surveillance, colonoscopy still essential.
- **Biopsies** Always take biopsies, since there is often disparity between endoscopic appearances and histology.
- **Radiology** Plain AXR useful for assessing faecal loading (particularly proximal constipation), and essential in severe flares for excluding toxic dilatation. Contrast barium radiology now superseded for assessing UC; in the case of an acutely tender abdomen and possible perforation, contrast CT gives much more information and shows colonic wall thickening and hyperaemia. Evolving role for other imaging techniques: in expert hands US can give useful though limited information about some areas of colon (including sigmoid and caecum), and there is interest in using MRI to characterize colitis (particularly given the absence of ionizing radiation).

Management

Medical

- See Box 4.78 for suggested treatment regimens for proctitis, mild disease, chronic active disease, and maintenance therapy, and Box 4.79 for acute severe UC.
- → CORTICOSTEROIDS reduce mortality of acute attacks from >35% to <1%, and are effective in ~70%.
- 5-ASAs (see → 5-AMINOSALICYLATES) significantly reduce relapse rate and improve quality of life. Several controlled trials confirm benefit of higher-dose delayed-release mesalazine. In moderately active UC, 4–4.8g/day associated with significantly higher rate of clinical remission. In addition, a combination of rectal plus oral ASA gives increased efficacy. There is also evidence that long-term 5-ASA reduces risk of colon cancer in UC. See ‘Drugs’ chapter for guidance on selecting between different preparations.

- → AZATHIOPRINE (AZA) and → 6-MERCAPTOPURINE (6-MP) are steroid-sparing agents, used for maintenance of remission in chronic active disease. Both generally safe and well-tolerated, but associated with potential toxicity that mandate screening and monitoring (see ➢ therapeutic drug monitoring in IBD). Meta-analysis of 30 non-controlled and 7 controlled studies found these were more effective than placebo. When only controlled studies were considered, absolute risk reduction was 23%, and number needed to treat to prevent one recurrence was 5.[3]
- → METHOTREXATE is another immunosuppressant, but there is currently insufficient evidence to recommend its routine use.
- → CICLOSPORIN has been widely used as rescue therapy in severe disease, with ~70% avoiding colectomy. However, there is a high relapse rate and, in the absence of further immunosuppression, most patients will subsequently come to colectomy.
- → INFLIXIMAB is a monoclonal antibody against TNF-α, used as an alternative to ciclosporin for rescue therapy (Box 4.79). Other anti-TNF medications, including adalimumab and golimumab are also effective in moderate-severe disease, although infliximab is probably still the anti-TNF of choice in acute severe colitis.
- → VEDOLIZUMAB is a monoclonal antibody against α4β7 integrin, and prevents lymphocyte trafficking into the GI tract. Currently it is most commonly used as 2nd line biologic therapy for patients who have had insufficient response, lost response or who did not tolerate anti-TNFs. However, there is increasing 1st line use, particular in patients where the safety profile of the anti-TNFs (particular with regards to infection) is a significant concern.
- → TOFACITINIB is a recently approved oral JAK1/3 inhibitor. It is typically used at high dose for induction (e.g. 10mg PO bd for 8wk) followed by a lower 5mg PO bd for maintenance. Due to concerns around its safety profile (particular infection and venous thrombosis), it is usually reserved for patients who have failed anti-TNFs.
- → USTEKINUMAB is an IgG monoclonal antibody to the p40 subunit of both IL-12 and IL-23. Has been licensed in ➲ Crohn's disease for some time. Recently licensed for 2nd line treatment in UC. Good safety record but precise role in drug sequencing will emerge over next few years.
- See also ➢ therapeutic drug monitoring in IBD for details on optimizing thiopurine and biologic medication.
- See Box 4.80 for other clinical pitfalls that can mimic treatment failure.

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[3] Gisbert JP (2009). *Aliment Pharmacol Ther* **30**: 126–37.

Box 4.78 Treatment regimens for mild-to-moderate UC

Proctitis Most respond to topical 5-ASA or steroid enemas, or a combination of both (e.g. Colifoam® enema in the morning and 5-ASA enema at night). Suppositories are effective for pure proctitis. If symptoms continue, add in oral 5-ASA.

Mild or moderately active disease Use oral mesalazine, oral steroids in moderate dose (prednisolone 20mg/day), and consider topical therapy if disease confined to left colon.

Chronic active disease Two flares within 12 months, or disease that relapses rapidly on tapering steroids, is an indication for starting 2nd-line treatment with an immunosuppressive agent. Persistent chronic disease in patients receiving steroids and immunosuppressive drugs should prompt consideration of biologic drugs or surgery.

Maintenance treatment Use mesalazine indefinitely in a dose of 1200–2400mg/day. Monitor renal function yearly because of low risk of interstitial nephritis (idiosyncratic rather than dose-related).

Surgical

Indications for surgery in ulcerative colitis include:

- Severe attacks not responding to medical therapy.
- Complications of severe attack (perforation, acute ➲ megacolon).
- Refractory chronic continuous disease with impaired quality of life.
- Dysplasia or carcinoma.

Choice of operation (see ➢ Clinical practice and diagnostics, p. 189):

- Total colectomy with permanent ileostomy.
- Total colectomy with ileo-anal pouch formation.

Colectomy with pouch formation is the operation of choice except for:

- Elderly.
- Patients with impaired sphincter pressures.
- Patients who do not wish to have a restorative proctocolectomy.

There may also be concerns in young patients of reproductive age as there is a 30% risk of impaired fertility (♂ and ♀), which is sometimes a reason for delaying pouch formation. Fuller consideration of issues around surgery for UC can be found in ➢ CPD, p. 190.

Complications, course, and prognosis

Most patients (80%) have intermittent attacks with varying durations of remission. A few have chronic continuous disease, and remainder have severe 1st attack with toxic megacolon or disease refractory to medical treatment requiring colectomy. Extent of the disease can change with time: about 20% with proctitis will extend after 10 years. Eventually up to 20% require colectomy.

Colorectal cancer surveillance

Disease extending beyond the rectum, as well as uncontrolled disease, is associated with a risk of malignant transformation. Risk relates principally to the duration and extent of disease of disease and, at 10 years post diagnosis, is significant enough to warrant regular colonoscopic screening. ➲ Primary sclerosing cholangitis and family history of colorectal cancer are additional high risk factors. See Box 4.81 for summary of guidance.[4]

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[4] Min MX *et al.* (2014). *J Clin Pharm Ther* **39**: 107–11.

❗ Box 4.79 Acute severe colitis

Treatment

Admit to hospital. Replace fluid and electrolyte losses. Give IV steroids (hydrocortisone 100mg qds) and SC LMWH (even if significant rectal bleeding). Continue oral nutrition. Treatment with IV steroids should continue for 5–7d if patient is improving, before switching to oral steroids (prednisolone 40mg OD, tapering by 5mg per week).

Predicting failure of medical therapy

Data from 1980s suggested that if mucosal islands, transverse colon dilatation >5.5cm or small intestinal loops >3cm visible on AXR, chance of needing colectomy >70%. Best recent data on prognosis in severe colitis from Travis *et al.*[5] The following, if present at day 3 after admission, give 85% prediction of needing surgery:

- Stool frequency >8 per day
- CRP >45mg/L in those passing 3–8 stools per day.

These factors are used by many clinicians to decide on need for rescue therapy.

Treatment options for rescue medical therapy

Choice in those not responding to steroids is between ciclosporin and infliximab. These are short-term medications, used while patient started on AZA or 6-MP, and steroids are tapered:

- **Ciclosporin** Continuous IV therapy at 2mg/kg for 5–7 d, then convert to oral therapy (5mg/kg in divided doses) for 3–6 months. Maintain trough levels at 100–200ng/ml.
- **Infliximab** 5–10mg/kg at weeks 0, 2, 6. While screening for various infections generally required before initiating anti-TNF therapy, usually inappropriate to avoid or delay rescue therapy in acute severe UC (if risk of TB, consider ciclosporin or surgery instead).
- **Ciclosporin versus Infliximab** The 1st trial comparing the two head-to-head (multicentre, open label RCT of 115 patients) did not find a difference in colectomy rates,[6] subsequently confirmed by the CONSTRUCT trial in 270 patients.

Indications for urgent colectomy

- Development of ➔ toxic megacolon (colonic diameter >6cm), which does not resolve or respond to steroids within 24h.
- Failure of rescue therapy with either ciclosporin or infliximab.

❗ Box 4.80 Pitfalls

- Check for proximal constipation above the inflammation: this is common and stops patients improving. Most clinicians treat with fibre but there is some evidence that an osmotic laxative such as macrogol (e.g. Movicol 204 sachets/d) should be used instead.
- ➔ Cytomegalovirus (CMV) is a potential reason for failure to respond to steroids. Ensure histology sent for CMV at time of endoscopy: infected cells contain typical 'owl's eye' inclusion bodies.

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[5] Travis SP *et al.* (1996). *Gut* **38**: 905–10.

[6] Laharie D *et al.* (2012). *Lancet* **380**: 1909–15.

Box 4.81 NICE guidelines on colonoscopic surveillance in UC

Offer to patients whose symptoms started 10 years ago, and disease extends beyond rectum.

Low risk: offer colonoscopy 5 yearly

- Extensive but quiescent UC, *or*
- Left-sided UC.

Intermediate risk: offer colonoscopy 3 yearly

- Extensive UC with mild active inflammation, *or*
- Post-inflammatory polyps, *or*
- Colorectal cancer in 1st degree relative, aged ≥50 years.

High risk: offer colonoscopy annually

- Extensive UC with moderate or severe active inflammation, *or*
- ➔ Primary sclerosing cholangitis, *or*
- Colonic stricture in past 5 years, *or*
- Any grade of dysplasia in the past 5 years, *or*
- Colorectal cancer in 1st degree relative aged <50 years.

Colitis in pregnancy

- Fertility is generally normal in women (in absence of abdominopelvic surgery), and not affected by disease or medication. Male sperm quality may be d by sulfasalazine, methotrexate, and infliximab.
- Flares of active disease in pregnant women should be treated as normal, and outcomes are generally optimal if conception occurs during remission. Women who have active disease at time of conception are more likely to have active disease during the pregnancy.
- Steroids, → 5-ASAs, and even → AZATHIOPRINE appear safe in pregnancy. → METHOTREXATE is teratogenic (in both men and women) and contraindicated. → INFLIXIMAB and → ADALIMUMAB are IgG1 antibodies and can cross placenta, particularly in 2nd or 3rd trimester. Both considered safe during 1st and 2nd trimesters.
- Pregnant women with UC are at higher risk of relapse during pregnancy and postpartum.[7]
- Disease has no overall adverse effect on developing foetus.

Guidelines

ECCO second European evidence-based consensus on the diagnosis and management of ulcerative colitis Parts 1, 2, and 3 (2012). 🖱 https://www.ecco-ibd.eu/index.php/publications/ecco-guidelines-science/published-ecco-guidelines.html.

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[7] Pedersen N *et al.* (2013). *Aliment Pharmacol Ther* **38**: 501–12.

Section 4

V

Vaccine use in immunocompromised *588*
Variceal bleeding: see ▲ **Acute upper GI bleeding** ▲ and ➲ Portal hypertension *588*
Vasculitis and the GI tract *588*
Veno-occlusive disease (VOD): see ➲ Sinusoidal obstruction syndrome (SOS) *589*
VIPoma: see ➲ Pancreatic endocrine tumours *589*
Viral hepatitis: see ➲ Hepatitis A–E *589*
Vitamins *590*
Volvulus *594*
Vomiting: see ► Approach to nausea and vomiting *595*

Vaccine use in immunocompromised

- Inactivated vaccines:
  - Generally effective, although responses may be diminished.
  - Where possible, administer before starting immunosuppression.
  - Vaccinations against diphtheria, tetanus, and pertussis; pneumococcus; influenza; meningococcus; ➔ hepatitis A and ➔ hepatitis B; and human papilloma virus safe and recommended for at-risk individuals, in line with national guidance.
- Live vaccines:
  - In general should avoid in immunocompromised, and pregnancy.
  - Measles, mumps, and rubella (MMR) and BCG vaccinations contraindicated if immunosuppressive therapy within 6wk.
  - Varicella zoster (VZV) vaccination safe and effective in patients on ≤3mg/kg/d azathioprine, ≤1.5mg/kg/d 6-MP, or ≤0.4mg/kg/wk methotrexate. Avoid in those receiving ≥20mg prednisolone (or equivalent) daily for ≥2 weeks, or anti-TNF therapy; in such individuals vaccinate at least 3wk prior to starting, or 3 months after discontinuing, these medications. Concomitant use of 5-ASAs theoretically increases risk of Reye syndrome (although no actual cases reported), so monitor carefully.[1] Inactivated vaccine against varicella zoster not available.
- Travel vaccines:[2]
  - ➔ Hepatitis A and ➔ Hepatitis B; Japanese encephalitis; meningococcal; and rabies vaccines all inactivated and safe.
  - Typhoid: use injectable (inactivated) over oral (live) vaccine.
  - ➔ Cholera: oral inactivated vaccine safe. Recommended for travel to endemic areas.
  - Yellow fever: only live vaccine available, and should probably be avoided due to (theoretical) risk of vaccine-induced encephalitis. Defer travel to endemic areas if possible.

Variceal bleeding

See: ▲ **Acute upper GI bleeding** ▲ and ➔ Portal hypertension.

Vasculitis and the GI tract

- GI vasculitides range in severity from acute self-limiting illnesses, to chronic diseases requiring long-term immunosuppression.
- Inflammation can affect splanchnic vessels of all sizes. Involvement of medium or large arteries (by e.g. ➔ polyarteritis nodosa, ➔ rheumatoid arthritis) may be confused with more common causes of ischaemia (thrombosis or embolism). Look for systemic features (renal involvement, cutaneous nodules, serum autoantibodies).

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[1] Lodhia N (2014). *J Clin Gastroenterol* **48**: 395–401.

[2] Patel RR *et al*. (2015). *Ther Clin Risk Manag* **11**: 217–28.

- Vasculitis typically caused by immune complex deposition in vessel walls, causing complement activation and inflammation resulting in aneurysm formation, vessel rupture, vascular occlusion, and fibrosis.
- Can present with bowel infarction, perforation, overt or occult GI bleeding, or vasculitic appendicitis. CT angiography/enterography, as well as direct angiography, helpful for diagnosing large and medium vessel vasculitis (Box 4.82).
- Treatment directed at underlying disorder. Frequently involves high-dose corticosteroids ± cyclophosphamide. In selected cases, IVIG or plasma exchange indicated.

Box 4.82 Diseases involving GI vasculitis

- ➲ Behçet's disease: orogenital ulceration, pathergy.
- ➲ Polyarteritis nodosa: aneurysm formation, often HBV +ve.
- ➲ Rheumatoid arthritis: RF, anticyclic citrullinated peptide Ab.
- ➲ Systemic sclerosis: ANA, anticentromere, antitopoisomerase Ab.
- ➲ Systemic lupus erythematosus: ANA, anti-dsDNA Ab, ↓ C3/C4.
- **Visceral arthritides**:
  - Churg–Strauss (triad of asthma, eosinophilia, and vasculitis; often p-ANCA/antimyeloperoxidase Ab +ve).
  - Granulomatosis with polyangiitis (pulmonary-renal syndrome, nasal symptoms, c-ANCA/antiproteinase-3 Ab +ve).
  - Cryoglobulinaemia.
  - ➲ Familial Mediterranean fever.
  - ➲ Henoch–Schönlein purpura.

Veno-occlusive disease (VOD)

See: ➲ Sinusoidal obstruction syndrome (SOS).

VIPoma

See: ➲ Pancreatic endocrine tumours.

Viral hepatitis

See: ➲ Hepatitis A–E.

Vitamins

Organic compounds, required in small (<100mg/d) quantities. Vitamins A, D, E, and K are fat-soluble.

Vitamin A (retinol)

Precursor (β-carotene) contains 2 retinol molecules, and is found in green vegetables and carrots. Retinol present in milk, eggs, and fish oils. Retinoids stored in hepatocytes and hepatic fat cells. Regulate many embryonic and adult genes through RXR and RAR transcription factors. Deficiency causes night blindness (as precursor of rhodopsin).

Diagnose if serum retinol <0.7μmol/L, although levels only ↓ when deficiency advanced as substantial hepatic stores. Can be falsely low during acute phase response, as retinol-binding protein ↓ transiently. Correct with 10,000IU/d oral replacement.

Vitamin B

- **B_1** is thiamine: see ➲ beriberi and ➲ Wernicke's encephalopathy.
- **B_2** is riboflavin. Deficiency causes sore tongue and mouth. Measure by RBC glutathione levels.
- **B_3** is niacin: see ➲ pellagra.
- **B_5** is pantothenic acid. Deficiency very rare, causes neuropathy.
- **B_6** is pyridoxine. Deficiency leads to dermatitis, glossitis, peripheral neuropathy, and sideroblastic anaemia.
- **B_7** is biotin. Deficiency causes dermatitis.
- **B_9** is ➲ folic acid.
- **B_{12}** is cobalamin.

Vitamin B_{12} (cobalamin)

- Essential co-factor in methylation reactions for DNA synthesis and cell metabolism, including methylmalonic acid homeostasis.
- Recommended intake 1.5μg/d. Standard Western diet contains 5–30μg, of which 1–5μg absorbed (see ➲ intrinsic factor). Found in animal sources; consequently ≈10% of vegetarians/vegans deficient.
- Bound to serum proteins as holohaptocorrin and holotranscobalamin. Total body stores 1–5mg, so deficiency takes years to develop.

Clinical features

Prevalence of deficiency 6% in <60y, and up to 20% in older patients. Causes of deficiency listed in Box 4.83. Manifestations include:

- **Mild deficiency**. Fatigue and megaloblastic anaemia.
- **Moderate deficiency**. Glossitis and sensory polyneuropathy.
- **Severe deficiency**. Pancytopaenia, subacute combined degeneration of the cord (sensorimotor polyneuropathy progressing to spastic ataxia), optic atrophy, dementia, psychosis, risk of cardiomyopathy.

❗ Pitfall

Clinical features of vitamin B_{12} deficiency can manifest without anaemia (up to 20% cases), and even without low serum cobalamin levels. In these cases, treatment should still be given without delay.

Box 4.83 Causes of cobalamin (vitamin B_{12}) deficiency

- Inadequate dietary intake:
  - Vegans.
  - Alcoholics.
- Inadequate release of food-bound cobalamin:
  - Achlorhydria.
  - → PROTON PUMP INHIBITORS, H_2 RECEPTOR ANTAGONISTS.
- Loss of active intrinsic factor (IF):
  - ➲ Pernicious anaemia.
  - ➲ Gastrectomy.
  - Congenital lack/abnormality of IF.
- Proximal small bowel disease and pancreatic disease:
  - ➲ Pancreatic insufficiency.
  - ➲ Gastrinoma.
  - ➲ Tropical sprue.
  - Small-bowel ➲ bacterial overgrowth.
  - Fish tapeworm *Diphyllobothrium latum* (rare).
- Ileal disorders:
  - Ileal resection.
  - ➲ Crohn's disease.
  - TB (see ➲ TB and the GI tract).
  - Lymphoma.
  - Dysfunctional uptake and use of cobalamin by cells: R binder deficiency, transcobalamin deficiency.
- Miscellaneous (rarely lead to clinical anaemia):
  - Pregnancy.
  - Thyrotoxicosis.
  - Erythroid hyperplasia.
- Drugs:
  - Colchicine.
  - Metformin.
  - PPIs, H_2RAs (see above).
  - Nitrous oxide (with chronic misuse).

Investigation

- Identifying vitamin B_{12} deficiency:
  - **Serum cobalamin**. 1st line, although no test ideal. Clinically normal level incompletely defined, though <200ng/L sufficiently sensitive to diagnose 97% of cases.
  - **Serum holotranscobalamin**. Currently 2nd line, although ↓ level more reliable than cobalamin in identifying deficiency.
  - **Plasma methylmalonic acid**. Where holotranscobalamin result intermediate, ↑ level confirms deficiency. Less reliable in elderly or in renal impairment.[3]
  - **FBC**. Shows ↓ Hb, ↑ MCV, reticulocytosis, and ↑ LDH. Patients with concomitant iron deficiency or thalassaemia trait may not develop typical morphological features.

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[3] Hunt A *et al.* (2015). *BMJ* **349**: g5226.

  - **Bone marrow biopsy** rarely required. Indicated where cause of macrocytosis unclear or inadequate response to supplementation.
- Identifying cause of deficiency:
  - If not vegan, do parietal cell and intrinsic factor antibodies to exclude ➔ pernicious anaemia.
  - If not detected, work up for causes listed in Box 4.83.
  - ➔ Schilling test now largely of historical interest.

Treatment

- Hydroxycobalamin IM 1mg 3/wk for 2 wk, then 1mg every 3 mo.
- High-dose (1–2mg/d) cyanocobalamin PO alternative in mild deficiency where compliance not an issue, or if IM not tolerated (🖱 Cochrane review: Oral vitamin B_{12} versus intramuscular vitamin B_{12} for vitamin B_{12} deficiency).
- Treat immediately if neurological features, and continue for up to 3wk or until no further improvement in symptoms.
- Also prescribe folate 5mg/d in all patients after vitamin B_{12} started.

Vitamin C (ascorbic acid)

Water-soluble. Dietary sources: fresh fruits, vegetables, liver. Deficiency causes scurvy: look for coiled body hairs, perifollicular haemorrhage, bruising, and gingivitis. Common in alcoholics. Can also occur in severe ➔ Crohn's disease or other mucosal enteropathies.

Vitamin D

Consists of two bioequivalent forms: vitamin D_2 (ergocalciferol, present in vegetables) and D_3 (cholecalciferol, synthesized in skin following sunlight exposure, or acquired through diet from oily fish and fortified foods such as dairy products). Both D_2 and D_3 biologically inactive without subsequent metabolism in liver and kidneys. Sunlight in northern climates can be insufficient to meet requirements, so nutritional intake critical at these times. Ingested vitamin D is fat-soluble and requires bile acids for absorption, before being packaged into chylomicrons by enterocytes. Subsequently undergoes 25-hydroxylation in liver, followed by 1-hydroxylation in kidneys, to form active 1,25-dihydroxy vitamin D.

Clinical features

Vitamin D enhances intestinal absorption of calcium, magnesium, phosphate, and zinc; promotes bone resorption and normal functioning of parathyroid hormone; and regulates immune function. Deficiency results in myalgia and proximal myopathy, hypocalcaemia, rickets (children), and osteomalacia (adults). Lowest concentration of vitamin D required to minimize hyperparathyroidism and maximize intestinal calcium transport is 30ng/ml of 25-OH vitamin D.

Low intake, fat malabsorption, bile salt deficiency, loss of absorptive surface, and impaired liver function are frequently seen in patients with GI disease, which may contribute to deficiency. Levels suboptimal in up to 70% of patients with ➔ Crohn's disease, 45% with ➔ ulcerative colitis, and significant minority with ➔ coeliac disease.

Investigation

Apart from ↓ plasma levels of vitamin D_2 and D_3, biochemical evidence for insufficiency includes ↑ serum PTH, urinary calcium <100mg/d, and ↑ urinary hydroxyproline. DEXA scanning useful to identify and monitor ↓ bone mineral density.

Treatment

- For vitamin D-deficient patients, dietary supplementation is inadequate. With exception of fatty fish, vitamin D content of most foods relatively low to non-existent.[4]
- Both ergocalciferol and cholecalciferol are available as oral supplements. Equally effective for treating and preventing disease.
  - Daily dosing of 800–2,000IU/d of either ≈ equivalent in studies.
  - D_3 has longer half-life. Preferred if dosing weekly or less often.
  - D_2 preferable if deficiency results from vegetarian or vegan diet.
- To correct severe deficiency, give loading dose of 50,000IU orally weekly, or 6,000IU/d, for 8 wk. Aim for blood level >30ng/ml. Follow with maintenance therapy of 1,500–2,000U/d.
- Long-term concurrent calcium supplementation usually unnecessary.
- Special circumstances:
  - ➔ Coeliac disease. Give all adults >50y with treated disease 800–1,000IU of D_3, and 1,200mg elemental calcium, daily. Aim to maintain serum levels of 25-OH vitamin D >30ng/ml.
  - In obese patients or severe malabsorption, very high doses may be needed. Start with 6,000–10,000IU/d (may need up to 50,000IU/d), followed by 3,000–6,000IU/d maintenance. An IM dose of 300,000IU monthly for 3 mo, followed by maintenance dose 1–2/y is an alternative. Monitor for toxicity.
  - PEG feeding. Ergocalciferol capsules contain D_2 in oil, which can clog tubes and should not be used. D_3 is a powder, and safe.

Vitamin E (tocopherol)

Found in grains, vegetables, and meats. Absorption requires intraluminal bile salts and pancreatic esterases. Vitamin packaged in chylomicrons and stored in liver and fat. Main role is antioxidant. Chronic cholestasis causes deficiency in children, leading to retinopathy, cerebellar ataxia, reduced vibration sense, and areflexia. ➔ Abetalipoproteinaemia causes similar syndrome because of failure to secrete chylomicrons. In adults, symptoms take years to develop, but can arise in any disease impairing fat absorption (ileal disease, impaired bile secretion, or intrahepatic diseases such as ➔ primary biliary cholangitis).

Vitamin K

Main dietary source is green vegetables. About 50% comes from gut bacterial synthesis. Diets deficient in vitamin K do not cause deficiency unless gut-sterilizing antibiotics given. Vitamin K deficiency may arise due to range of GI diseases, including chronic cholestasis (e.g. ➔ primary biliary cholangitis) and ➔ coeliac disease. Diagnosis suggested by elevated prothrombin time (PT)/INR in appropriate clinical setting. In patients with suspected liver failure, vital to give parenteral vitamin K to exclude deficiency as cause of elevated PT.

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[4] Holick MF *et al.* (2011). *J Clin Endocrinol Metabol* **96**: 1911–30.

Volvulus

Twisting of gut around one axis, causing luminal occlusion and sometimes strangulation. Can affect colon or stomach.

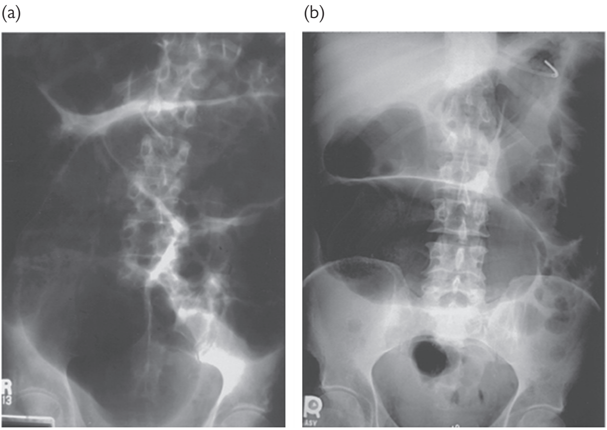

Fig. 4.23 AXR of sigmoid (left) and caecal (right) volvulus. On left, dilated segment comes from pelvis towards RUQ. On right, caecum extends from right lower abdomen across midline. Reproduced from Feldman M *et al*. (2003). *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, with permission from Elsevier.

Colonic volvulus

Can occur where there is a loop of bowel that is movable in the peritoneal cavity with close approximation of fixation points, most common sigmoid colon (75%) or caecum (20%) (Fig. 4.23). Rarely may affect transverse colon and splenic flexure. History of chronic constipation and laxative use common. Patients with sigmoid volvulus often elderly (mean age: 70) and abdominal tenderness only in minority. Presents with slowly progressive abdominal pain and superimposed colic (due to peristalsis), nausea, constipation, and abdominal distension.

Management

- **Sigmoid volvulus**.
  - Endoscopic decompression of colon with placement of rectal tube into obstructed segment works in ~75–95%. Risk of recurrence 40–50%, so definitive surgical treatment following successful decompression should be considered.
  - In patients deemed high risk from general anaesthesia, percutaneous endoscopic colopexy is alternative. A colonoscope is inserted into the left colon until transillumination is seen through skin surface, and finger pressure indents colon. Under local anaesthetic, two standard 16-Ch PEG tubes are pushed through abdominal wall into

  bowel, then secured against abdominal wall to anchor sigmoid colon in two places. Colonoscope reinserted to check final position of catheters, which are then attached to drainage bags and flushed twice daily. Current evidence base limited to small case series. Peritonitis secondary to tube migration or faecal contamination during procedure is described, so requires peri-procedural antibiotic cover.
  - Strangulated sigmoid volvulus, or patients with signs of peritonitis, require emergency laparotomy with end colostomy.
- **Caecal volvulus**. Colonoscopic decompression can be successful, but risk of perforating thinned ischaemic caecum higher. Best surgical option controversial, but right hemicolectomy often performed.
- Overall mortality approaches 10%. Major predictive factor is gangrenous bowel (up to 60% mortality), which occurs in ~20%.

Gastric volvulus

Rare. Most common in 5th decade. Usually associated with diaphragmatic hernia, phrenic nerve paralysis, or kyphoscoliosis. Stomach may twist around long (60%) or short (40%) axis. With volvulus around long axis, patients commonly present acutely, with upper abdominal or retrosternal pain and unproductive retching; gastric infarction can follow. Volvulus around short axis more likely to be incomplete and intermittent, and present with chronic symptoms.

☠ Acute gastric volvulus is an emergency with a high mortality (30–50% untreated). NG intubation at bedside indicated as initial treatment to decompress stomach. If unsuccessful, endoscopic NG tube placement may be required. Most patients with gastric volvulus require some form of repair. Surgery (open or laparoscopic) is more definitive as allows repair of anatomical abnormalities. Endoscopic gastrostomy (PEG) tubes can be placed to anchor stomach, but anatomic abnormality cannot be addressed by endoscopy.

Vomiting

See: ► Approach to nausea and vomiting.

Section 4

W

Weil's disease: see ➔ Leptospirosis *598*
Wernicke's encephalopathy (WE) *598*
Whipple's disease *598*
Whipworm *599*
Wilson's disease *600*

Weil's disease

See: ➲ Leptospirosis.

Wernicke's encephalopathy (WE)

- Results from ➲ vitamin B_1 (thiamine) deficiency. Predominantly found in malnourished patients with ➲ alcohol use disorder or ➲ alcoholic liver disease (reduced hepatic thiamine storage capacity), and may be mistaken for intoxication (see ▶ Approach to agitation and confusion in the GI patient). Can also occur in patients with anorexia nervosa, hyperemesis gravidarum, and prolonged starvation.
- Clinical triad (only present in 30%) of ophthalmoplegia (horizontal nystagmus, conjugate gaze palsy, fixed pupils, paralysis of lateral rectus muscles), ataxia (wide-based cerebellar gait, with vestibular dysfunction), and cognitive impairment (apathy, spatial disorientation, global confusion).
- Diagnosis usually clinical, but in cases of uncertainty red cell transketolase ↓, and thiamine levels can now be measured directly.
- Potentially fatal untreated: 80% will develop Korsakoff psychosis, characterized by retrograde and anterograde amnesia, confabulation, and mammillary body atrophy on neuroimaging (MRI brain).
- Give parenteral vitamins B and C for rapid correction of severe depletion (e.g. Pabrinex® I and II tds IV/IM for 3d), followed by thiamine 100mg bd PO + vitamin B Co-strong 2 tablets bd PO for 10d. Maintenance thiamine 100mg bd if ongoing poor nutritional state.
- WE may be precipitated by high carbohydrate load (e.g. IV glucose in hospital), so vital to administer thiamine if any clinical suspicion of deficiency. Check serum magnesium, and treat if low as thiamine may be ineffective with hypomagnesaemia.

Whipple's disease

Named after George Whipple (1878–1976) who described disease in 1907. Suggested role of bacteria (but not proven until 1997). Won Nobel Prize for work on ➲ pernicious anaemia.

- Systemic infection caused by Gram-positive *Tropheryma whipplei*. Incidence 0.5/million. Tends to affect middle-aged men (♂:♀ 8:1), 30% of whom in farming-related trades. Oral acquisition presumed.
- Infected people have subtle immune defects in Th1 function, but whether this predisposes to, or is a consequence of, disease unclear.

Clinical features

Biphasic disease, with early phase of fever and arthralgia/arthritis, and late phase affecting several organ systems, including:

- **GI tract** Malabsorption with gradual weight loss, diarrhoea (steatorrhoea or watery stool), and abdominal pain. Occult blood loss, and mesenteric and retroperitoneal adenopathy are common.

- **Central nervous system** 10–40% of patients. Progressive dementia, ophthalmoplegia, and psychiatric symptoms. CSF usually normal, although *T. whipplei* PCR can be positive.
- **Cardiovascular** Endocarditis, myocarditis, or pericarditis.
- **Musculoskeletal** Seronegative polyarthralgia is common.

Investigation

- **Endoscopy** White or yellow patches due to lipid deposits may be seen at upper GI endoscopy. Multiple duodenal biopsies essential. Histology shows swollen macrophage cytoplasm containing many lysosomes stuffed with *T. whipplei*; these stain positive with PAS. Immunohistochemistry improves sensitivity. Disorders mimicking histology of Whipple's disease uncommon but include *Mycobacterium avium* and histoplasmosis.
- **PCR** Sensitive, though can be positive in healthy carriers. Confirm diagnosis by histology, or 2nd positive PCR from another site (e.g. synovial fluid or CSF).

Treatment and prognosis

Initial response to antibiotics is rapid (diarrhoea resolves within days, arthralgia within weeks, weight gain within 1–2 months). Tetracyclines were initially used, but relapses affecting CNS are common and difficult to treat. Current recommendations are for ceftriaxone 2g IV od or meropenem 1g IV tds for 14d, followed by oral trimethoprim-sulfamethoxazole 960mg bd for 1y (although evidence emerging this can be abbreviated).[1] Relapse rate ~5%.

Whipworm

Trichuris trichiura is a roundworm of phylum *Nematoda*. Adult reaches 3–5cm and has lifespan 1–3y. Mostly tropical distribution: highest rates in Asia, followed by Africa then South America. Estimated worldwide infection rate 800 million. Organism spread via faecal–oral route, and humans sole hosts. Embryonated eggs ingested, then released larvae travel to colon where they burrow into epithelium and mature within 12 weeks. Adult worms live preferentially in caecum, although in heavy infections are seen throughout colon and rectum. Inflammation at site of mucosal attachment causes colitis, which can mimic ➔ inflammatory bowel disease.

Clinical features

- Usually asymptomatic, but heavy infestation may cause lower abdominal discomfort, diarrhoea, anaemia, and clubbing.
- *Trichuris* dysentery syndrome rare: characterized by bloody diarrhoea, tenesmus, rectal prolapse, and anaemia.

Investigation

Stool microscopy for *T. trichiura* eggs.

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[1] Feurle GE *et al.* (2013). *J Infect* **66**: 263–70.

Treatment

Mebendazole 100mg bd for 3d or albendazole 400mg stat dose.

💣 Controversy. Therapeutic use of *Trichuris* in inflammatory bowel disease

Trichuris induces strong T_h2 response, and attenuates T_h1 reactions. This has led to experimental administration of pig whipworm to patients with inflammatory bowel disease. Two randomized controlled trials reported to date, in ➔ Crohn's disease and ➔ ulcerative colitis. Both promising in terms of safety and efficacy for inducing remission, though most recent Cochrane review (2014). 🖱 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009400.pub2/abstract;jsessionid=09E537EE7FA06E63076860D07B844740.f04t01 grades evidence as insufficient to recommend use at present.

Wilson's disease

Background

- Autosomal recessive disorder. Incidence 1/30,000 live births. Caused by mutations in *ATP7B* gene on chromosome 13, which encodes the Wilson's disease protein (WDP) ATPase transporter.
- In healthy individuals, ~10% of the 1–2mg/d ingested copper is absorbed, and bound to serum albumin. After transport to hepatocytes, WDP incorporates copper into caeruloplasmin allowing its release back into bloodstream (90% of circulating copper in this form) or excretion into bile.
- Mutations in *ATP7B* impair both functions of WDP, resulting in accumulation of copper in tissues and subsequent oxidative damage.

Clinical features

- May present at any age, but majority of patients 5–55 years.
- Clinical features listed in Table 4.41. Liver disease is the most common presentation in childhood. Chronic hepatitis may be similar to ➔ autoimmune hepatitis.
- ▲ **Acute liver failure** ▲ often associated with haemolysis. First presentation may be with complications of cirrhosis. ➔ Gallstones occur due to recurrent haemolysis (mechanism remains unclear).
- Neuropsychiatric presentation usual in adolescence/early adulthood. Kayser–Fleischer rings (Box 4.84. and Plate 37) rarely absent in patients with neurological disease.

Investigations

Diagnosis rarely made unless considered, and biochemical parameters may be inconsistent, particularly in patients with liver disease. No test result should be viewed in isolation, and diagnosis usually made through combination of clinical picture and highly suggestive results (see '❗ Pitfalls' below). **Unexplained liver disease in a young person with Coombs-negative haemolytic anaemia should raise suspicion.**

- LFTs non-specific, but ALT usually <1,500U/L, even in acute liver failure. ↑ Bilirubin may also be caused by haemolysis.
- Slit-lamp examination for Kayser–Fleischer rings (Box 4.84).

Box 4.84 Kayser–Fleischer rings

- Copper deposits in Descemet's membrane in peripheral cornea.
- Best visualized on slit lamp. Appear brown with blue iris, grey with brown iris. Do not always form complete rings: deposits start at 12 o'clock position, then 6 o'clock, then spread laterally.
- May be accompanied by sunflower cataract (deposition in lens).
- Present in 95% of patients with neurological Wilson's disease, but absent in up to 50% of pre-symptomatic patients or pure hepatic disease. Fade following treatment with chelating agents.
- Seen rarely in other conditions of chronic cholestasis (e.g. ➔ primary biliary cholangitis).
- Can get false Kayser–Fleischer rings composed of melanin (distinguish on slit lamp as pigment homogenous, not granular, and not in Descemet's membrane).

- Plasma caeruloplasmin <0.2g/L in 85% of cases.
- Serum copper <11μmol/L.
- 24h urinary copper >1.6μmol/24 hours.
- ➢ Liver biopsy. Hepatic copper >250μg/g dry weight (normal <50μg/g). Liver histology may show necrosis, chronic hepatitis, or cirrhosis. Suggestive features include fatty change, Mallory hyaline, copper staining, and vacuolated nuclei.
- Genetic analysis (recommended for 1st degree relatives of patients).

Table 4.41 Clinical features of Wilson's disease

System	Features
Liver	Acute hepatitis, ▲ **acute liver failure** ▲
	Decompensated cirrhosis, portal hypertension
	➔ Gallstones
Neurological	Behavioural change, cognitive impairment
	Parkinsonism, tremor
	Dysarthria, dystonia, dysphagia
Renal	Renal tubular acidosis
	Renal calculi
Musculoskeletal	Arthropathy
	Osteoporosis
	Osteomalacia
Haematological	Haemolytic anaemia (Coombs-negative)
Ophthalmic	Kayser–Fleischer rings, sunflower cataracts
Other	Cardiomyopathy
	Pancreatitis

- Combination of Kayser–Fleischer rings with serum caeruloplasmin <0.1g/L is sufficient to establish diagnosis. The Wilson's scoring system can be used to help improve the diagnostic certainty.[2]
- MRI brain should be considered prior to treatment of neurologic disease, and in all patients in whom this diagnosis is possible.

Management

- Acute liver failure. Manage as for ▲ **acute liver failure** ▲ and transfer to specialist liver unit for ➲ liver transplantation.
- Liver disease without liver failure:
  - Avoid foods with high copper content (e.g. chocolate, shellfish).
  - Penicillamine (20mg/kg/d) with pyridoxine 25mg/d promotes urinary copper excretion, with good prognosis. Treatment adequacy monitored with 24h urinary copper measurement. Goal is increased excretion and normal serum copper.
  - Trientine (300mg tds) is an alternative.
  - Zinc (150–300mg/d) reduces copper uptake from GI tract.

Guideline

EASL Clinical Practice Guidelines on Wilson's disease (2012). 🖱 http://www.easl.eu/assets/application/files/e793d591ec4de1c_file.pdf.

❗ Pitfalls. Caveats in diagnosing Wilson's disease

Kayser–Fleischer rings	Copper deposition is seen in other cholestatic liver diseases
↓ Caeruloplasmin	Acute phase reactant, so may be falsely ↑ in Wilson's disease with active liver inflammation, as well as falsely ↓ in other chronic liver diseases due to ↓ synthesis (nevertheless, caeruloplasmin <140mg/L is 100% sensitive and specific for Wilson's disease)
↓ Serum copper	May ↑ due to leakage of non-caeruloplasmin-bound copper from necrotic liver in acute Wilson's disease. Can be high in patients with cholestasis
Liver histology	Copper staining may be negative, despite raised liver copper concentrations
Genetic analysis	Three most common mutations in UK patients only account for 30% of patients

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[2] EASL (2012). *J Hepatol* **56**: 671–85.

Section 4

Y

Yersinia 604

Yersinia

Gram-negative bacilli. *Y. enterocolitica* causes gastroenteritis and mesenteric adenitis. Other species that now rarely result in human disease are *Y. pestis* (plague) and *Y. pseudotuberculosis* (causes granulomatous inflammation of terminal ileum, liver, spleen, and lymph nodes, mimicking ➲ Crohn's disease). Siderophilic, so patients with ➲ haemochromatosis are more susceptible. May disseminate in the immunocompromised.

Y. enterocolitica invades epithelium overlying Peyer's patches (especially in terminal ileum) then spreads to lamina propria. Food-borne pathogen: epidemics associated with contaminated meat products (especially pork), milk, and ice cream.[1] Rare (0.1 culture-confirmed case/100,000 people/year). Two-thirds of cases are enterocolitis. Children under 4 most frequently affected. Associated mesenteric adenitis is common and may be confused with appendicitis; ultrasound can help differentiate. Usually self-limiting, although erythema nodosum, erythema multiforme, and reactive polyarthritis can emerge 1–2 weeks after diarrhoea onset.

Diagnosis

Infrequently suspected unless complicated by extraintestinal features. May be identified on stool culture (although detection rates low and not routinely tested in many laboratories), mucosal biopsy, or resection specimen following presumed appendicitis. Specific IgA antibodies found in blood (peak 7–28 days post-infection).

Treatment

Usually diagnosed late, when antibiotics probably do not alter course of GI infection. In severe cases, treat with 3rd generation cephalosporin, ciprofloxacin (avoid in children), co-trimoxazole, or a tetracycline.[2]

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[1] Drummond N *et al.* (2012). *Foodborne Pathog Dis* **9**: 179–89.

[2] Zheng H *et al.* (2008). Eur J Clin Microbiol Infect Dis **27**: 741–52.

Z

Zieve’s syndrome *606*
Zollinger–Ellison syndrome: see ➔ Gastrinoma *606*

Zieve's syndrome

Triad of jaundice, hyperlipidaemia, and transient haemolytic anaemia, occurring in patients with alcoholic steatohepatitis. First described by Leslie Zieve in 1957 in 20 male patients.[1] Most have upper abdominal/RUQ pain and macrocytic anaemia. Hypercholesterolaemia and jaundice resolve within 3 weeks if patient stops drinking. Exact mechanism of haemolysis not known, but may involve several acquired cellular defects (including acquired pyruvate kinase deficiency or instability, and membrane alterations).[2]

Zollinger–Ellison syndrome

See: ➔ Gastrinoma.

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[1] Zieve L (1958). *Ann Intern Medicine* **48**: 471-96.

[2] Piccini J *et al*. (2003). *American Journal of Medicine* **115**: 729–31.

Section 5

Drugs used in gastroenterology and hepatology

Acetylcysteine (NAC) *608*
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Ustekinumab *647*
Vedolizumab *647*

Acetylcysteine

GI indication	➔ Paracetamol overdose, and some other forms of ➔ drug-induced liver injury.
Mode of action	Precursor of reduced glutathione, so replenishes hepatic glutathione stores. Antioxidant effects.
Dose/duration	Dosed according to body weight category. See ➔ paracetamol overdose.
Contraindication	Anaphylaxis (rare). ❗ More common 'anaphylactoid' reactions result from mast cell histamine release, not IgE, and ∴ should not preclude re-exposure if clinically needed. Can pre-treat these patients with antihistamine and ↓ rate of infusion.
Side effects	Anaphylactoid and allergic reactions (urticaria, angio-oedema), nausea, and vomiting.
Practice points	If anaphylactoid reaction, stop infusion temporarily and treat with antihistamine, then restart at slower rate.

Aciclovir

GI indication	➔ Herpes simplex (usually stomatitis or perianal; oesophageal or colonic in immunocompromised) and varicella zoster.
Mode of action	Purine nucleoside analogue. Not a substrate for human thymidine kinase, so non-toxic to mammalian host cells. Phosphated aciclovir is a substrate for, and inhibitor of, DNA polymerase, preventing further viral DNA synthesis.
Dose/ duration	200mg (400mg in immunocompromised) PO 5 times daily, or 5mg/kg IV tds for 5d.
Side effects	Acute kidney injury (crystal nephropathy), usually reversible with rehydration.
Practice points	↓ Frequency of administration in renal impairment (eGFR <50ml/min).

Adalimumab

See → ANTI-TNF DRUGS (p. 613).

5-Aminosalicylates (5-ASA)

(e.g. mesalazine, olsalazine, balsalazide, sulfasalazine).

GI indication	Treatment of mild-to-moderate ➲ ulcerative colitis and ➲ collagenous colitis). Maintenance of remission and chemoprophylaxis in ➲ ulcerative colitis. Evidence for efficacy in ➲ Crohn's disease is weak, although no trials powered to look for efficacy in different disease distributions (e.g. Crohn's colitis).
Mode of action	Not fully understood. *In vitro* low concentrations ↑ prostaglandin production while higher concentrations ↓ PGE_2 production. *In vitro* inhibition of leukotrienes may not be physiologically relevant. Also ↓ IL-1 release and alter HLA-DR expression.
Formulation	Rapid absorption in upper GI tract has led to development of several carrier systems to allow 5-ASA drug delivery to different sites in colon and small intestine (see Table 5.1).
Dose/ duration	Treatment dose is up to 4.8g/d. All mesalazine preparations can be taken once daily. Maintenance dose 1.2–2.4g/d. Concurrent administration of rectal 5-ASA up to 2g/d more effective in patients with distal inflammation.
Contraindications	Sensitivity to salicylates. Caution in CKD.
Side effects	• May cause diarrhoea and headache. • Renal toxicity due to interstitial nephritis. • Blood dyscrasias. • Rarely associated with pancreatitis, allergic lung reactions, and lupus-like syndrome. • Sulfasalazine can cause Stevens–Johnson syndrome, and oligozoospermia in ♂.
Practice points	Choice of preparation depends largely on differences in site of action of drug (see Table 5.1). Sulfasalazine effective and cheap, but side effects in 15% (mostly due to the sulfapyridine component). Newer 5-ASAs have better side effect profile but olsalazine can cause secretory diarrhoea (effect that may possibly be useful if proximal constipation associated with distal colitis). Pentasa® is 5-ASA of choice for small intestinal involvement. Balsalazide may be more effective in left-sided colitis. Choose formulation based on cost and lowest number of tablets, which maximizes patient concordance.

Table 5.1 Classification of the aminosalicylates

pH dependent	
Asacol®	Mesalazine coated in Eudragit-S, dissolving at pH >7. Used for colonic disease.
Salofalk®	Mesalazine coated in Eudragit-L, dissolving at pH >6. May release in terminal ileum.
Microspheres	
Pentasa®	Microgranules of 5-ASA. Release starts in stomach and duodenum. 60% released in small intestine; remainder should be available in colon.
Prodrugs	
Sulfasalazine (Salazopyrin®)	5-ASA conjugated by diazo bond to sulfapyridine, thought to be responsible for many side effects.
Olsalazine (Dipentum®)	Two 5-ASA molecules linked by diazo bond.
Balsalazide (Colazide®)	5-ASA linked to 4-aminobenzoylalanine.

Antacids and alginates

- Often used in ulcer dyspepsia and non-erosive gastro-oesophageal reflux. Evidence of efficacy in non-ulcer dyspepsia uncertain.
- Usually contain compounds of aluminium (constipating) or magnesium (laxative). Bismuth-containing antacids should be avoided because absorption can cause neurotoxicity, and often constipating. High doses of calcium-containing antacids can cause hypercalcaemia and alkalosis.
- A few antacids contain simethicone, an antifoaming agent that can ↓ flatulence. Can also be used in relief of hiccups in palliative care.
- Alginates are antacids that form raft to float on surface of stomach contents to ↓ reflux.
- Sodium content of antacids varies widely and may be a factor affecting prescribing in chronic liver disease.

Antibiotics

Antibiotic selection should be based where possible on prior culture and sensitivity to optimize response and ↓ ever-increasing problem of resistance. Many GI-related infections are due to Gram-negative or anaerobic bacteria. Choice of antibiotics described here are limited to, those commonly used in GI practice. See → CEPHALOSPORINS, → CIPROFLOXACIN, → GENTAMICIN, → GLYCOPEPTIDES (teicoplanin and vancomycin), → METRONIDAZOLE, → PENICILLINS (amoxicillin, co-amoxiclav, flucloxacillin, and piperacillin-tazobactam).

Anticholinergics

(e.g. hyoscine hydrobromide).

GI indication	Nausea; motion sickness; premedication.
Mode of action	Inhibit muscarinic acetylcholine receptors.
Dose/duration	Hyoscine hydrobromide 300μg PO before journey, or transdermal patch 1mg/72h.
Contraindication	Urinary retention, GI obstruction, porphyria, cardiac disease, closed-angle glaucoma.
Side effects	Drowsiness, dry mouth, blurred vision, urinary retention.

Antidiarrhoeal agents

- Mostly antimotility agents, such as opioids and loperamide. Absorbents such as kaolin not recommended for acute diarrhoea.
- Antimotility agents should not be used where inhibition of peristalsis may be dangerous, such as acute ➔ ulcerative colitis or ➔ antibiotic-associated diarrhoea.
- In severe secretory diarrhoea, → OCTREOTIDE, → PROTON PUMP INHIBITORS, and clonidine may be tried, in addition to conventional antimotility agents. Clonidine is an α_2 receptor agonist that may be used for diarrhoea related to opiate withdrawal or diabetes. May cause postural hypotension.

Antiemetics/antinausea drugs

- → H_1 RECEPTOR ANTAGONIST antihistamines effective but may cause drowsiness and antimuscarinic effects. Phenothiazines block chemoreceptor trigger zone and useful in treating nausea associated with cancer, radiation, and drugs such as anaesthetic agents, opioids, and cytotoxics.
- → DOPAMINE RECEPTOR ANTAGONISTS (domperidone, metoclopramide) very useful for treating nausea and vomiting associated with gastroduodenal and biliary disease. Prokinetic, so agents of choice in gastroparesis, but contraindicated if GI obstruction. Acute dystonic reactions (treat with procyclidine 5–10mg IV/IM) and extrapyramidal side effects mean not recommended for use beyond 5d, or in children.
- → SEROTONIN (5-HT_3) RECEPTOR ANTAGONISTS (e.g. ondansetron) very effective for postoperative and cytotoxic-associated nausea.
- → LORAZEPAM effective for anticipatory nausea in patients receiving chemotherapy.
- → DEXAMETHASONE useful for managing nausea associated with general anaesthesia or chemotherapy.

Table 5.2 Antidiarrhoeal drugs

Drug	**Mechanism of action**	**Side effects**
Opiates (morphine, codeine phosphate)	Alter motility. Possibly antisecretory	May precipitate toxic megacolon, CNS, and respiratory depression, delayed gastric emptying. Addictive potential.
Antimotility (loperamide) and anticholinergics (e.g. co-phenotrope, a mixture of diphenoxylate and atropine 100:1)	Reduce motility: loperamide has calmodulin-binding and calcium-channel blocking activity	Similar to → OPIOIDS ± → ANTICHOLINERGICS.
Bismuth subsalicylate	Bactericidal: suspended in clay, which might bind enterotoxins	Black stools and black tongue, salicylate toxicity.
Bulk-forming agents (ispaghula, methylcellulose)	Hydroscopic and ↑ stool viscosity. Used to control faecal consistency in ileostomy effluent	Bloating and flatus.
Adsorbents (kaolin)	Hydroscopic, may bind enterotoxins. Not recommended for acute diarrhoea	
Colestyramine, aluminium hydroxide	Bind bile acids	Bind drugs and vitamins.

- Aprepitant is a neurokinin receptor antagonist used as an adjunct to dexamethasone in preventing nausea and vomiting associated with highly emetogenic chemotherapy.

Antifungals

- Gastroenterologists often treat candidal infections, and may be involved in treating patients with *Cryptococcus*, *Histoplasma*, and *Aspergillus*. May also manage patients with ➔ drug-induced liver injury due to antifungal drugs (e.g. itraconazole, ketoconazole).
- Amphotericin and nystatin belong to polyene family. Neither absorbed when given orally but useful in treatment of oral or intestinal candidiasis. Fluconazole well absorbed orally and also penetrates CSF, making it useful for treating fungal meningitis.
- For *Candida*, use fluconazole 50–100mg/d PO for 7–14d or nystatin 100,000 units every 6h.

Antihistamines

See → H_1 RECEPTOR ANTAGONISTS for antiemetics, and → H_2 RECEPTOR ANTAGONISTS (H_2RAS) for antacids.

Antispasmodics

Drugs used for GI smooth muscle spasm include antimuscarinics (atropine, dicycloverine, hyoscine) and direct relaxants (alverine, mebeverine, peppermint oil). All of these may relieve pain in ➔ irritable bowel syndrome and ➔ diverticular disease; take ~20min before meals. Avoid antimuscarinics in angle-closure glaucoma, myasthenia, paralytic ileus, pyloric stenosis, and prostatic enlargement. Suggested medications include:

- Peppermint oil 1–2 capsules PO tds.
- Mebeverine 135–150mg PO tds.
- Hyoscine butylbromide. Start at 10mg PO tds. Can escalate to 20mg qds if needed.

Anti-TNF drugs

(e.g. infliximab, adalimumab, golimumab).

GI indication	• Severe active ➔ Crohn's disease and ➔ ulcerative colitis in patients not responding, or intolerant, to steroids ± thiopurines/methotrexate. • Refractory fistulating Crohn's disease. • Maintenance therapy can be considered for those responding to initial induction course.
Mode of action	Monoclonal antibodies against TNF-α. Infliximab is chimeric (25% mouse, 75% human); adalimumab and golimumab (only licensed for ➔ ulcerative colitis) are fully humanized. TNF receptor analogues (e.g. etanercept) and monoclonal fragments (certolizumab) less effective, potentially as they lack ability to activate Fc receptors and induce cell death or modulate macrophage biology through this pathway.
Dose/duration	• **Infliximab**. Initially 5mg/kg by IV infusion, followed by further doses at 2 and 6 weeks, and every 8 weeks thereafter. May need to escalate to 10mg/kg if non-response or development of neutralizing antibodies. • **Adalimumab**. Initially 160 mg SC, followed by 80mg after 2wk. Maintenance dose 40mg every 2 weeks, increased if necessary to weekly administration. • **Golimumab**. Initially 200mg SC, followed by 100mg after 2wk. Maintenance 50mg (weight <80kg) or 100mg (weight >80kg) every 4wk. • In patients on maintenance therapy, regular dosing is better than intermittent dosing (increases risk of anti-drug antibodies developing).

Contraindication	• Active infection, tuberculosis. Patients must be evaluated for active or latent TB before treatment (e.g. CXR, tuberculin test, IFN-γ release assay). • Heart failure. Discontinue if symptoms develop or worsen. Avoid in severe heart failure.
Side effects	Infusion site and acute hypersensitivity reactions; infection (including TB). Lupus-like syndrome and demyelination recognised but rare.
Practice points	• Prophylactic hydrocortisone 100–200mg IV ↓ risk of acute reaction. Risk of hypersensitivity ↑ if interval >16wk between infusions. • Data from ACCENT 1 study do not support early caution about anti-TNF causing strictures via mucosal healing and fibrosis, and suggest higher doses of infliximab associated with lower rates of stricturing. • In patients with severe mucosal ulceration (e.g. severe acute UC), significant GI losses of monoclonal antibodies can occur, which may explain lack of efficacy in some patients, and can be overcome by ↑ dose. • Stopping rules for patients who have achieved remission with anti-TNFs still poorly defined. STORI study showed that 50% of patients in deep remission could stop; many of these patients relapse if followed-up long-term, but remain sensitive to re-induction.

Azathioprine

GI indication	• Steroid-dependent inflammatory bowel disease, fistulating ➲ Crohn's disease. Combination with anti-TNF minimizes antibody development and maximizes response (SONIC trial), although ↑ rate of infection. • Other autoimmune conditions such as ➲ autoimmune hepatitis, and maintenance of remission in ➲ autoimmune pancreatitis/IgG4-related disease.
Mode of action	Metabolized *in vivo* to → MERCAPTOPURINE, then to ➤ thioguanine nucleotides that inhibit DNA synthesis. See ➲ thiopurine methyltransferase (TPMT).

Dose/duration	2–2.5mg/kg/d. Takes up to 3–4mo to become fully effective. IV loading does not speed response. Duration of therapy not established. Maintenance therapy for at least 4y in patients with IBD safe. Early fears over ↑ incidence of immunoproliferative disorders not substantiated. Recent data from some European registries (CESAME) raise concerns about incidence of non-melanoma skin cancer, which is tending to limit duration of use in younger patients.
Contraindications	Hypersensitivity, absent TPMT.
Side effects	Nausea, malaise, dizziness, myalgia in ~15%. Leukopaenia in 4%, severe (WCC <2) in 1%; not solely related to TPMT genotype. Can cause acute ➔ drug-induced liver injury (usually cholestatic; centrizonal changes on histology) and pancreatitis (5%). Also associated with ➔ sinusoidal obstruction syndrome.
Practice points	• At least some intolerance (nausea, malaise, dizziness) relates to nitro-imidazole ring that differentiates azathioprine from → MERCAPTOPURINE. Arguably all patients should be given latter rather than azathioprine. • Reduce dose by 75% if giving concurrent xanthine oxidase inhibitors, such as allopurinol, which shunts metabolites towards thioguanines and away from toxic methylmercaptopurine. • Leukopaenia can develop after prolonged therapy. Measure WCC weekly for 4wk, monthly for 3mo, and then every 3mo. Low counts usually respond to stopping treatment for few weeks and adjusting dose. • See also ➔ TPMT and ▷ therapeutic drug monitoring in IBD.

Bismuth

Effective in healing ➔ peptic ulceration (Pepto-Bismol ® 10ml PO bd). Also role as 2nd-line (and increasingly 1st-line) agent in ➔ *Helicobacter* eradication, usually as part of quadruple therapy with 2 antibiotics + → PROTON PUMP INHIBITOR. May darken tongue and blacken faeces. Should not be given for >12wk as risks of neurotoxicity and encephalopathy.

Botulinum toxin

GI indication	➔ Achalasia.
Mode of action	Produced by *Clostridium botulinum*. Blocks acetylcholine release from pre-synaptic neuromuscular junction. Reduces tone at gastro-oesophageal junction.
Dose/duration	Injection using sclerotherapy needle of 80 units of botulinum toxin A (20 units/ml injected into each of four quadrants) at level of lower oesophageal sphincter.
Contraindication	Hypersensitivity.
Side effects	Transient chest pain in 25%. Gastro-oesophageal reflux. Oesophageal perforation or mediastinitis rare. Long-term safety unknown.
Practice points	Intrasphincteric botulinum toxin provides short-term relief in 60–90%, but majority have recurrence at <1y. Subsequent injections less effective. Generally reserved for older patients, and poor candidates for ▷ endoscopic dilatation or surgery.

Bowel cleansing solutions

See: ▶ ‘Bowel preparation’, p. 196.

Cannabinoids (e.g. nabilone)

GI indication	Antiemetic, used during cytotoxic chemotherapy, particularly if unresponsive to conventional treatments.
Mode of action	Unclear, but may act on brainstem nuclei.
Dose/duration	Nabilone 1–2mg PO bd.
Contraindications	Pregnancy/breastfeeding, severe liver impairment. Caution in those with psychiatric disease.
Side effects	Drowsiness, vertigo, mood disturbance, psychosis, abdominal pain. Enhanced effects of alcohol.
Practice points	Advise patients of potential effects on driving and skilled tasks.

Carvedilol

GI indication	Prophylaxis against variceal bleed in patients with ➔ portal hypertension.
Mode of action	Non-cardioselective β and α1-adrenergic receptor blocker. Reduces portal pressure through ↓ in portal and collateral blood flow.
Dose/duration	3.125mg-12.5mg. Start at low dose and ↑ as systemic BP and HR allow.
Contraindication	Bradycardia, hypotension, 1st-degree heart block, asthma. Caution in heart failure as negative inotrope.
Side effects	Bradycardia, hypotension, fatigue, impotence, cold hands. Reduces warning signs of hypoglycaemia.
Practice points	Effective primary and secondary prophylaxis (cheaper, safer, and easier than variceal band ligation, but compliance uncertain). Checking resting heart rate useful means of assessing drug response/compliance (aim for 25% ↓ in heart rate).

Cephalosporins

(e.g. cefotaxime, ceftazidime, ceftriaxone, cefuroxime).

GI indication	➲ Spontaneous bacterial peritonitis, intra-abdominal sepsis, ➲ oesophageal rupture, variceal haemorrhage (see ▲ **acute upper GI bleeding** ▲), ➲ cholangitis, pyogenic ➲ liver abscess. Often in combination with → METRONIDAZOLE (for better anaerobic cover).
Mode of action	Bactericidal β-lactam antibiotic. Inhibits synthesis of peptidoglycan. Active against Gram-negative and (to lesser extent) Gram-positive bacteria.
Dose/duration	Cefuroxime 750mg-1.5g IV tds. Cefotaxime 1–2g IV bd. Ceftriaxone 1–2g IV od (over 2–4min).
Contraindications	Penicillin hypersensitivity—10% cross-reactivity. However, always check what is meant by 'penicillin allergy'—history of urticaria/angio-oedema clearly more relevant than diarrhoea, and may influence use of cephalosporin. Caution in renal impairment.
Side effects	Nausea, vomiting, ➲ *C. difficile*-associated diarrhoea, rash, headache, fever, abnormal liver function tests (cholestatic picture).
Practice points	Calcium salt of ceftriaxone may deposit in gallbladder, occasionally giving symptoms, but usually resolves on stopping drug.

Ciclosporin

GI indication	Severe ➲ ulcerative colitis. Commonly used in those not responding to steroids by 3rd day of admission. Less used now because of UK (CONSTRUCT) and European (CYSIF) trials showing no difference in efficacy between ciclosporin and infliximab – most clinicians now have more experience of anti-TNF. Not effective in ➲ Crohn's disease. ➲ Liver transplantation.
Mode of action	Prevents T cell activation by inhibiting calcineurin pathway.

Dose/duration	In IBD, initial trials used 4mg/kg/d IV, but 2mg/kg/d equally effective. Oral preparation (Neoral®) 5mg/kg/d may be as effective.
Contraindication	Renal impairment. Monitor cholesterol and magnesium levels before starting.
Side effects	Main toxicities are renal and neurological. Can cause hypercholesterolaemia, eosinophilic colitis, hypertension, hyperuricaemia, hypertrichosis, gingival hyperplasia, tremor, and cutaneous squamous cell carcinoma.
Practice points	Opportunistic infections can occur and some centres use prophylactic co-trimoxazole. Ciclosporin may delay but not prevent need for colectomy. Many centres couple its use with long-term azathioprine started on discharge from hospital. Patients on steroids, ciclosporin, and azathioprine are heavily immunosuppressed and need very close supervision; steroids should be weaned over 6wk, followed by weaning ciclosporin as azathioprine takes effect. Dose reduction of 25–50% required if creatinine ↑ by >30% above baseline on treatment.

Ciprofloxacin

GI indication	➔ Traveller's diarrhoea, ➔ cholangitis, ➔ spontaneous bacterial peritonitis prophylaxis.
Mode of action	Quinolone, active against Gram-negative and (to lesser extent) Gram-positive bacteria. Bactericidal; blocks bacterial DNA replication by binding DNA gyrase.
Dose/duration	Ciprofloxacin 500mg PO or 400mg IV bd.
Contraindications	Caution in pregnancy/breastfeeding, myasthenia gravis.
Side effects	Nausea, vomiting, dyspepsia, ➔ *C. difficile*-associated diarrhoea, photosensitivity, rash (rarely Stevens–Johnson syndrome), urticaria. Increases blood levels of theophyllines and enhances effects of warfarin. Rarely associated with Achilles tendonitis and tendon rupture.
Practice points	Few indications for IV rather than oral administration, but bioavailability of oral preparation may be significantly ↓ by concomitant use of enteral feeds.

Colestyramine, colesevelam

GI indication	• Pruritus related to biliary obstruction (e.g. ➔ primary biliary cholangitis, ➔ primary sclerosing cholangitis). • Diarrhoea/steatorrhoea due to ➔ bile acid malabsorption. • ➔ Obstetric cholestasis.
Mode of action	Anion-exchange resin. Binds bile acids, forming insoluble complex, and preventing reabsorption.
Dose/duration	• Colestyramine ◦ Pruritus: 4g sachet mixed with water 1–2/d. ◦ Bile acid diarrhoea: 3–6 sachets/d in 2–4 divided doses. • Colesevelam: 2–6 capsules/d in divided doses.
Contraindications	• Complete large duct biliary obstruction (this requires instrumental relief, e.g. ERCP). Pruritus due to this is unlikely to respond to bile acid binding agents. • Absorption of wide range of drugs affected by bile salt binding agents (e.g. ➔ oral contraceptive pill, digoxin, levothyroxine), so give these >1h before or >4h after.
Side effects	Abdominal discomfort, nausea, constipation, diarrhoea. Interference with fat-soluble vitamin absorption (➔ vitamins A, D, E, K) may require monitoring and supplementation.
Practice points	Most effective given before and after breakfast (time of maximal gallbladder emptying and thus bile acid binding). May paradoxically worsen diarrhoea if >100cm ileum resected (see ➔ bile acid malabsorption).

Corticosteroids

(e.g. prednisolone, hydrocortisone, budesonide).

GI indication	➲ Crohn's disease, ➲ ulcerative colitis, unresponsive ➲ coeliac disease, ➲ liver transplantation, ➲ autoimmune hepatitis, ➲ autoimmune pancreatitis/IgG4-related disease.
Mode of action	Immunosuppressive and anti-inflammatory. Inhibit pro-inflammatory cytokines (e.g. IL-1, IL-2, IFN, TNF), adhesion molecules, MHC class II molecules, elastase, collagenase, and nitric oxide synthase.
Dose/duration	Preparation, dose, route, and duration depend on clinical indication. Examples: • Prednisolone 30–40mg PO od (initial treatment of ➲ ulcerative colitis, ➲ Crohn's disease, ➲ autoimmune hepatitis). • Hydrocortisone 100mg IV qds (severe acute ➲ ulcerative colitis/➲ Crohn's disease) – equivalent to ~80mg/d oral prednisolone. • Budesonide 9mg PO od, reducing dose over 8wk (active ileal/right colon ➲ Crohn's disease). • Rectal prednisolone PR od (proctitis, rectosigmoid ➲ ulcerative colitis).
Contraindications	Ongoing sepsis (unless antimicrobial therapy also given). Avoid live vaccines if high-dose steroids.
Side effects	Most side effects relate to dose and duration. Fewer systemic effects with rectal steroids (and budesonide) than with oral prednisolone, but occur with all. • GI. Dyspepsia; ➲ peptic ulceration (causative role of steroids still debated, but prophylactic → PROTON PUMP INHIBITORS often given if long-term steroids used + other risk factor present); oral/oesophageal ➲ candidiasis, ➲ acute pancreatitis. • Infection. May mask systemic sepsis/TB (but negligible ↑ risk if equivalent of prednisolone <10mg/d). • Musculoskeletal. Growth impairment (but in children with Crohn's disease this is more due to disease than treatment), bone loss (additive risk with ➲ Crohn's disease and ➲ coeliac disease); proximal myopathy, skeletal avascular necrosis.

	• Endocrine. Adrenal suppression, Cushing's syndrome, amenorrhoea, diabetes mellitus, hypertension. • Skin. Bruising, atrophy, striae, acne. • Eye. Glaucoma, cataract. • CNS. Euphoria, depression, psychosis, insomnia.
Practice points	• Patients should be given steroid card. • Exclude bone loss and consider prophylaxis in patients on long-term steroids (see ⊳ 'bone densitometry', p. 167 and ➲ osteoporosis). • Rectal steroids best self-administered just before going to bed, as more likely to be retained. • Steroid-sparing agents (e.g. → AZATHIOPRINE) often indicated after disease remission obtained. • Stepwise withdrawal of steroids if >7.5mg prednisolone taken for >3wk. • Increased neutrophil count during steroid treatment may relate to ↑ immature cells from bone marrow, ↑ circulating half-life, and ↓ vascular margination, but always consider sepsis. • Steroid equivalents: 5mg prednisolone ≡ 4mg methylprednisolone ≡ 20mg hydrocortisone ≡ 750mcg dexamethasone.

Cromoglicate

Mast cell stabilizer. Proposed for use in hypersensitivity reactions to food and some cases of ➲ irritable bowel syndrome. Also used by some paediatricians in management of inflammatory bowel disease where there is predominance of eosinophils or allergic component.

Role in IBS controversial as no good evidence symptoms caused by type I hypersensitivity or of ↑ incidence of IBS in atopic patients. However, sodium cromoglicate (e.g. 100–200mg before meals) has been used (with and without exclusion diets) in patients with reported food intolerance and higher success rates found in those with positive skin-prick reactions to food extracts. Studies were neither blinded nor adequately controlled, and principle remains unsubstantiated.

Daclatasvir

GI indication	➲ Hepatitis C.
Mode of action	NS5B polymerase inhibitor. Antiviral action against genotype 1 and 3 disease.
Dose/duration	60mg OD for 12–24wk. Must be used with → SOFOSBUVIR.
Side effects	Headache, fatigue, and nausea (<5% patients).
Practice points	Dose reduction (30mg) required in patients taking atazanavir/ritonavir. Dose increase (90mg) required in patients taking efavirenz.

Dopamine (D_2) receptor antagonists

(e.g. prochlorperazine, domperidone, metoclopramide).

GI indication	Nausea and vomiting, especially with non-ulcer dyspepsia, ➲ GORD, and ➲ gastroparesis where prokinetic effect may be beneficial.
Mode of action	Antagonize D_2 receptor in central chemoreceptor trigger zone. Metoclopramide also antagonizes 5-HT_3 and 5-HT_4 receptors, and has both central and peripheral action.
Dose/duration	Domperidone 10–20mg PO tds. Metoclopramide 10mg PO/SC/IM/IV tds. Prochlorperazine 10mg PO tds; 12.5mg IM stat.
Contraindications	Pregnancy/breastfeeding, phaeochromocytoma, bowel obstruction.
Side effects	Drowsiness, dystonic reactions (especially with fast IV bolus; less prominent with domperidone), hyperprolactinaemia, neuroleptic malignant syndrome (metoclopramide, prochlorperazine). Can ↑ QT interval so caution in cardiac disease or with other drugs that also do this.
Practice points	These drugs ↑ lower oesophageal sphincter tone and speed gastric emptying. Metoclopramide only recommended for short-term use in adults.

Ganciclovir

GI indication	Active ➔ cytomegalovirus infection.
Mode of action	Synthetic analogue of guanine. Inhibits viral replication.
Dose/duration	5mg/kg IV bd for 14–21d.
Contraindication	Pregnancy, hypersensitivity.
Side effects	Leukopaenia, anaemia, thrombocytopaenia.
Practice points	Do not give if neutrophils $<0.5 \times 10^9$/L. Dose reduce in renal impairment (eGFR <70mL/min).

Gentamicin

GI indication	Severe intra-abdominal infection/septicaemia, ➔ cholangitis (usually in addition to other agents).
Mode of action	Bactericidal aminoglycoside. Binds bacterial ribosomal subunit, leading to tRNA misreading, impairing protein synthesis. Particularly effective against Gram-negative bacteria. Hydrophilic, achieving high intravascular concentrations; ∴ useful for bacteraemia/sepsis.
Dose/duration	3–7mg/kg/d IV od. Doses up to 240mg given by slow injection over 3–5min; larger doses by 30–60min infusion.
Contraindications	Caution and dose reduction in renal impairment.
Side effects	Dose-related hearing, vestibular, and renal toxicity. Nausea, rash.
Practice points	Monitoring of dose essential. Take plasma concentration 6–14h after 1st dose and review nomogram to plan further dose adjustments. Repeat daily if varying renal function; otherwise every 3–5d. Extended dosing interval (every 36h or 48h) and dose reduction may be necessary. Liaise with pharmacist/microbiologist.

Golimumab

See → ANTI-TNF DRUGS (p. 613).

Glycopeptides

(e.g. teicoplanin, vancomycin).

GI indication	IV: Staphylococcal infection, including MRSA. Oral: ➔ C. *difficile*.
Mode of action	Inhibits cell wall synthesis.
Dose/duration	*Teicoplanin* 400mg IV bd for 3 doses; then ↓ to OD. Reduce dose in renal failure. *Vancomycin* • Staphylococcal disease: 1g BD IV; monitor plasma concentrations. • C. *difficile*: 125mg PO qds for 10–14d. Can ↑ to 250mg or 500mg if severe infection.
Contraindications	Renal impairment, auditory impairment, known hypersensitivity.
Side effects	Renal failure, blood dyscrasia, GI disturbance. Rapid infusion associated with histamine release: 'red man syndrome'. Ototoxicity with vancomycin occurred with older preparations, secondary to contaminant.
Practice points	• Oral vancomycin does not normally cross GI mucosal barrier. Exception in inflammatory bowel disease, where systemic absorption may occur. • Monitor renal function daily with IV use and adjust dose accordingly. Plasma concentrations should be monitored, with pre-dose trough concentration of 10–15mg/L. Oral vancomycin does not require monitoring of levels. Teicoplanin usually does not require monitoring of levels, although can occasionally be helpful in patients with renal failure.

H_1 receptor antagonists

(e.g. cinnarizine, cyclizine, promethazine).

GI indication	General nausea, motion sickness, vestibular disorders.
Mode of action	Antagonism of histamine H_1 receptors.
Dose/duration	Cinnarizine 15–30mg PO tds. Cyclizine 50mg PO/SC/IM/IV tds. Promethazine 25mg PO od.
Contraindication	Avoid promethazine in ➔ porphyria, and cyclizine in severe heart failure.
Side effects	Drowsiness, ↑ effect of alcohol, dry mouth, blurred vision, tachycardia. IV cyclizine has abuse potential.
Practice points	Advise patients of potential effects on driving and skilled tasks.

H_2 receptor antagonists (H_2RA)

(e.g. cimetidine, ranitidine, nizatidine, famotidine).

GI indication	• ➔ Peptic ulceration. • Gastro-oesophageal reflux: less effective than → PROTON PUMP INHIBITORS (PPIs), but may have synergistic effects on resting parietal cell acid output and so often combined in difficult or refractory cases. • ↓ Incidence of bleeding gastric erosions in ▲ **acute liver failure** ▲.
Mode of action	↓ Gastric acid output by histamine receptor blockade.
Dose/duration	Ranitidine 150mg bd PO or 300mg at night. Cimetidine 400mg bd PO or 800mg at night.
Contraindication	Caution in severe liver and renal impairment.
Side effects	• Diarrhoea. • Altered liver function. • Cimetidine associated with gynaecomastia and inhibits cytochrome P450. Avoid in patients on warfarin, phenytoin, or theophylline.
Practice points	In clinical practice, PPIs have largely replaced H_2RAs as 1st line agents in controlling gastric acid.

Infliximab

See → ANTI-TNF DRUGS (p. 613).

Interferon alfa

GI indication	Replicating chronic ➲ hepatitis B, ➲ hepatitis C.
Mode of action	Activates innate immune antiviral pathways.
Dose/duration	➲ Hepatitis B eAg$^+$ disease: e.g. pegylated interferon (PEG-IFN) A2a: 180μg/wk for 48wk. ➲ Hepatitis C: Used in combination with ribavirin, e.g. PEG-IFN A2a 180μg/wk or PEG-IFN A2b 1.5μg/kg/wk, + → RIBAVIRIN 800–1,200mg/d (duration dependent on viral and patient factors).
Contraindication	Severe depression, decompensated cirrhosis, autoimmune disease, ischaemic heart disease, diabetic retinopathy, pregnancy, renal transplant.
Side effects	Influenza-like symptoms (fatigue, fever, arthralgia, headache), psychiatric problems, weight loss, myelosuppression (usually neutropaenia), hypotension/arrhythmias, hair loss, abdominal pain.
Practice points	In hepatitis C, use largely replaced by direct-acting antivirals (DAA). Influenza symptoms 6–8h after dose respond well to paracetamol and usually improve on repeat doses. Blood monitoring (especially neutrophils) needed weekly for 1st 3wk, then monthly. Neutrophils <1.5 x 10^9/L requires dose reduction; <1 x 10^9/L requires cessation.

Lamivudine

GI indication	Prophylaxis against chronic ➔ hepatitis B reactivation for patients having chemotherapy/ immunosuppression. No longer used for primary treatment due to resistance.
Mode of action	Nucleoside analogue. Inhibits viral reverse transcriptase, suppressing HBV replication.
Dose/duration	100mg PO od. Duration dependent on duration of immunosuppression and type/duration of chemotherapy.
Contraindication	None, but use with other antiretrovirals if patient co-infected with HIV, to avoid HIV escape mutants.
Side effects	May lead to ALT flare on discontinuation.

Laxatives

- **Bulking agents** (bran, methylcellulose, ispaghula) relieve constipation by ↑ faecal mass, which stimulates peristalsis.
- **Stimulant** laxatives include bisacodyl, docusate, senna, and picosulfate. Prolonged use may cause atonic colon and hypokalaemia.
- **Stool softeners**, such as paraffin, can cause anal seepage and possibly a granulomatous reaction following absorption of small amounts.
- **Osmotic laxatives** ↑ amount of water in large bowel. Include saline purgatives such as magnesium hydroxide, and phosphate enemas. Lactulose is a disaccharide that is not absorbed; produces osmotic diarrhoea of low faecal pH, which inhibits proliferation of ammonia-producing organisms and therefore used in ▲ **hepatic encephalopathy** ▲. Macrogols are inert polymers of polyethylene glycol that sequester fluid in bowel.
- Prucalopride is a **5-HT$_4$ receptor agonist** that facilitates cholinergic and non-adrenergic non-cholinergic neurotransmission. Increases small and large bowel transit. Placebo-controlled trial suggests efficacy in both slow and normal transit constipation.

Laxative	Usual dose	Side effects and comments
Bulk forming		
Psyllium, methylcellulose	4–7g	Useful for small hard stools. Need to ↑ fluid intake. Impaction can occur above strictures.
Emollient		
Mineral oil	15–45ml	May ↓ fat-soluble vitamin absorption. Can cause lipid aspiration pneumonia. Do not give in dysphagia, to debilitated, or at bedtime.
Docusate salts	Up to 500mg daily in divided doses	Anionic surfactants that soften stool and stimulate fluid secretion.
Hyperosmolar		
Polyethylene glycol solutions	Macrogols 1–3 sachets/d Klean-Prep® 1–4L/d	Often used as bowel preparation for colonoscopy, but can be very useful in treating intractable constipation. Macrogols need to be prescribed for regular administration, not prn, for efficacy in constipation.
Lactulose	15–60mL PO	Metabolized by colon bacteria to low molecular weight compounds that ↑ stool osmolarity. Can cause bloating.
Glycerol	5–15ml enema	Given intrarectally—may produce rectal irritation.
Saline		
Magnesium salts		Avoid in renal failure due to magnesium absorption and possible toxicity.
Stimulant		
Castor oil Diphenylmethane (bisacodyl) Anthraquinones (senna)		Hydrolysed by lipases to ricinoleic acid, which stimulates secretion and motility. Cause fluid and electrolyte accumulation in colon. Particularly effective for opioid-induced constipation. Absorbed by small intestine, metabolized by the liver. Can cause melanosis coli and degeneration of myenteric plexus.
5-HT_4 receptor agonist		
Prucalopride	2mg PO od	Useful in chronic constipation when other approaches have failed.

Ledipasvir

GI indication	➔ Hepatitis C genotype 1.
Mode of action	NS5A inhibitor.
Dose/duration	90mg OD 12–24wk. Needs to be used with → SOFOSBUVIR.
Side effects	Fatigue and headache.
Practice points	Drug-drug interactions with St John's wort and rifampicin (↓ blood concentrations of ledipasvir).

Linaclotide

GI indication	Constipation-predominant ➔ irritable bowel syndrome.
Mode of action	Activates guanylate cyclase receptor on intestinal epithelial cells, stimulating secretion of chloride, bicarbonate, and water into intestinal lumen.
Dose/duration	290µg PO od.
Contraindication	Avoid in GI obstruction and inflammatory bowel disease.
Side effects	Abdominal bloating, diarrhoea, flatulence.

Mercaptopurine

GI indication	Steroid-dependent inflammatory bowel disease, fistulating ➲ Crohn's disease, and other autoimmune conditions such as ➲ autoimmune hepatitis.
Mode of action	Metabolized to thioguanine nucleotides that inhibit DNA synthesis. Lacks nitro-imidazole side chain found in → AZATHIOPRINE, which may explain its generally better side effect profile.
Dose/duration	Dose of mercaptopurine in inflammatory bowel disease is 1–1.5mg/kg/d. Takes up to 3–4mo to become fully effective. Optimal duration of therapy not established.
Contraindication	Hypersensitivity: absent ➲ TPMT levels.
Side effects	Nausea, malaise, dizziness, myalgia, bone marrow suppression, pancreatitis.
Practice points	See → AZATHIOPRINE. Now routine to check ➲ TPMT, thioguanine nucleotides (TGN) and methylmercaptopurine (MMP) levels (see ▷ therapeutic drug monitoring in IBD).

Methotrexate

GI indication	Steroid-dependent ➔ Crohn's disease, often in those unable to tolerate thiopurines. Steroid-dependent ➔ ulcerative colitis in those intolerant to thiopurines.
Mode of action	Folate antagonist, inhibiting nucleotide synthesis, although relevance of this questioned as usually given with folic acid. Also inhibits IL-1, IL-2, IL-6, and IL-8.
Dose/duration	Best trial used 25mg IM once weekly for 16wk. If effective, can be converted to 15mg/wk for maintenance.
Contraindication	• Pre-existing liver or pulmonary disease (seek advice). • Teratogenic: both ♂ and ♀ should be informed of risks to gametogenesis. Crosses into breast milk. • Extensively protein bound: can be displaced by salicylates, diuretics, sulphonamides, tetracyclines, ↑ plasma levels. • NSAIDs ↓ renal excretion and may enhance toxicity.
Side effects	Can cause hepatic fibrosis and interstitial pneumonitis.
Practice points	• Monitor FBC and LFT before starting treatment, weekly until stabilized, then every 3 mo. • Routine liver biopsy no longer advised. • Give folic acid 5mg/d for 5 days of week (avoiding methotrexate day and following day), to prevent stomatitis and nausea.

Metronidazole

GI indication	• ➲ Amoebiasis. • ➲ *C. difficile*. • ➲ Cholangitis. • ➲ Diverticular abscess. • ➲ Giardiasis. • ➲ *H. pylori* (in combination with other agents). • ➲ Perianal Crohn's disease. • Pyogenic ➲ liver abscess.
Mode of action	Imidazole ring-based antibiotic. Active against anaerobic bacteria and protozoa.
Dose/duration	Depends on indication. Examples: • Pseudomembranous colitis: 400mg tds PO for 10d. • Cholangitis: 500mg IV tds for 7–10d (with 3rd-generation → CEPHALOSPORIN).
Contraindications	Alcohol—causes disulfiram-like reaction.
Side effects	Nausea, vomiting, metallic taste, rash, headache, drowsiness, dizziness, abnormal LFTs, jaundice, peripheral neuropathy (with prolonged use), leukopaenia. May ↑ toxicity of warfarin, phenytoin, lithium.
Practice points	In patients with ➲ *Helicobacter pylori*, ~50% metronidazole resistance and common reason for failure of eradication therapy.

Misoprostol

Prostaglandin analogue with antisecretory and gastroprotective properties. Can prevent NSAID-associated ➲ peptic ulceration, but use limited by side effect profile (diarrhoea very common with doses >200µg). Absolutely contraindicated in pregnancy: causes miscarriage.

Nitrates

Use of topical nitrate (glyceryl trinitrate 0.2–0.4% ointment) speeds healing of anal fissures but can cause systemic effects from vasodilatation (e.g. headache) in ~30%. Nitrates have also been used in management of oesophageal spasm: in uncontrolled trials, ↓ pain and improve manometric parameters in some patients. Diltiazem ointment 2% also effective in anal fissure, with fewer side effects. Currently no convincing difference between GTN and diltiazem.

Obeticholic acid (OCA)

GI indication	• ➔ Primary biliary cholangitis when response to → URSODEOXYCHOLIC ACID inadequate (use in combination), or not tolerated (can use as monotherapy).
Mode of action	Semi-synthetic bile acid analogue.
Dose/duration	5mg PO od for 6mo, then increase to 10mg od if necessary/tolerated
Contraindications	Complete biliary obstruction.
Side effects	Arthralgia, constipation, pruritus.

Octreotide

GI indication	• Metastatic ➔ carcinoid tumours, ➔ pancreatic endocrine tumours (especially VIPoma). • Acute variceal bleeding (if terlipressin not available). • High output stomas/fistulae.
Mode of action	Mimics action of natural hormone—inhibits insulin, splanchnic blood flow, and gut hormones (e.g. glucagon, gastrin), and ↓ gut motility.
Dose/duration	Octreotide 50µg SC tds ↓ diarrhoea in 50–83%, and flushing in 50–100%. May be increased, depending on response. Long-acting octreotide LAR® 10–30mg SC monthly also effective. Can be given by dilute IV injection if rapid relief required but needs cardiac monitoring.
Contraindications	• Contraindicated with ciclosporin. • May require dose adjustment of hypoglycaemic drugs. • Pregnancy.
Side effects	• Abdominal symptoms in 5–10% (diarrhoea, pain, nausea), with ↑ risk of gallstones and biliary complications due to gallbladder hypomotility. • Dysglycaemia. • Cardiac arrhythmia (e.g. bradycardia) reported. • Alopecia.
Practice points	• Case reports of benefit in pancreatic fistulae. • Evidence of benefit in acute variceal bleeding inconclusive. Most hepatologists only use as pharmacotherapy if contraindication to → TERLIPRESSIN.

Opiates

(e.g. codeine, tramadol, pethidine, fentanyl, morphine, oxycodone).

GI indication	• ▲ **Acute abdominal pain** ▲. • Severe chronic pain not controlled by other measures (e.g. ➲ chronic pancreatitis, abdominal malignancy). • Sedation for endoscopy. • Weak opiates may help control diarrhoea.
Mode of action	Act at various sites centrally (e.g. periaqueductal grey matter) and peripherally (e.g. peripheral afferent terminal) on range of opiate receptors, and thought to facilitate endogenous release of endorphins and encephalins.
Dose/duration	Preparation and dose depend on severity and cause of pain. Stepwise approach to ⊳ pain control (see p. 136) may include increasing from milder (e.g. codeine, tramadol) to more potent (e.g. morphine, fentanyl) opiates. Examples: • Codeine phosphate 30–60mg PO 4–6 hourly. • Dihydrocodeine 30mg 4–6 hourly. • Tramadol 50–100mg 4–6 hourly. • Morphine sulfate 2.5–20mg PO, IM, IV, SC 2–6 hourly as required. When converting oral to parenteral, halve dose. Can titrate to pain, e.g. give another dose after 10min if still in pain. IV/SC continuous infusion: 0.8–10mg/h. • Fentanyl 25–100μg IV, 25–75μg transdermal patch (lasts 72h).
Contraindication	Known hypersensitivity. Caution in respiratory depression. May precipitate ▲ **hepatic encephalopathy** ▲ in patients with significant liver disease.
Side effects	• Respiratory and CNS depression. • Vomiting, ↓ gastric emptying, and gut hypomobility. • Itching. • Dependence, addiction.

Practice points

- Involve pain team early—in most UK hospitals, most experienced in advising appropriate regimens.
- Dosing requirements may vary widely in an individual patient, and dose of opiate given should only be that sufficient to relieve pain. Chronic users acquire tolerance and may require higher doses.
- When selecting weak opiate, codeine requires metabolism to morphine by CYP450 2D6; up to 10% of population are weak metabolizers so if apparent lack of analgesic effect consider switching to dihydrocodeine (less dependent on this pathway).
- Tramadol said to be less constipating than codeine/dihydrocodeine. ❗ Inhibits 5-HT reuptake and can precipitate serotonin syndrome in combination with other serotonergic drugs. Lowers seizure threshold, so avoid if possible in patients with epilepsy.
- Oxycodone and fentanyl said to be better handled in renal failure, although evidence of difference in clinically meaningful outcomes weak.

Orlistat

Lipase inhibitor that ↓ absorption of dietary fat. Used in conjunction with low calorie diet in obesity management. Indications are ➔ body mass index >30kg/m², or >28kg/m² in presence of other risk factors (such as type 2 diabetes, hypertension, or hypercholesteraemia). Not licensed for use longer than 2y. Dose is 120mg with each meal (maximum 360mg/d). Side effects: steatorrhoea, incontinence, and pain if fat intake not reduced. NICE guidance (2006) 🖱 https://www.nice.org.uk/guidance/cg189. recommends only continuing beyond 3mo if weight loss >5% from start of treatment.

Pancreatic enzyme supplements

(e.g. Creon®, Pancrease®, Nutrizym®).

GI indication	➔ Pancreatic insufficiency (e.g. due to ➔ chronic pancreatitis, ➔ cystic fibrosis, or extensive pancreatic resection).
Mode of action	Replaces deficient pancreatic enzymes, allowing digestion of starch, fat, and protein.
Dose/duration	Most patients given inadequate doses. While Creon® 10,000 two capsules with meals, one with snacks often recommended, most require more (e.g. Creon® 40,000 or equivalent for adequate replacement).
Contraindications	Fibrosing colonopathy with high-dose supplements in children with ➔ cystic fibrosis, but not seen in adults, or with Creon® 25,000 or less.
Side effects	Nausea, abdominal discomfort. Perianal irritation at high dose.
Practice points	Give pancreatic supplements with → PROTON PUMP INHIBITOR to ↓ inactivation by gastric acidity. Faecal elastase measurement (see ▷ 'pancreatic function tests', p. 153) provides good indicator of exocrine insufficiency, and assay not affected by concomitant pancreatic supplements. Allow several days between dose adjustments.

Penicillins

(e.g. amoxicillin, co-amoxiclav, piperacillin).

GI indication	• Amoxicillin, co-amoxiclav: ➤ antibiotic prophylaxis prior to endoscopic procedures, ➲ *H. pylori* eradication. • Piperacillin: severe intra-abdominal infection/septicaemia (usually used as 2nd-line therapy). Infective episodes after ➲ liver transplantation. Active against Gram-positive, Gram-negative aerobic and anaerobic bacteria, and *Pseudomonas*.
Mode of action	Bactericidal through inhibition of cell wall synthesis. Co-amoxiclav contains β-lactamase inhibitor clavulanic acid. Tazocin® contains piperacillin and β-lactamase inhibitor tazobactam.
Dose/duration	• Amoxicillin: 500mg-1g PO/IV tds. • Co-amoxiclav: 625mg PO, 1.2g IV tds. • Piperacillin-tazobactam: 4.5g IV tds.
Contraindications	Penicillin hypersensitivity (but check what is meant by this—non-specific antibiotic-related diarrhoea should not preclude use for life-threatening sepsis, but angio-oedema/anaphylaxis clearly should).
Side effects and interactions	Rash, urticaria, anaphylaxis, nausea, vomiting, diarrhoea, ➲ pseudomembranous colitis, ➲ drug-induced liver injury, interstitial nephritis.
Practice points	High doses ↑ serum Na^+, and can be associated with encephalopathy and seizures.

Prokinetics

- → METOCLOPRAMIDE and → DOMPERIDONE are dopamine receptor antagonists that stimulate gastric emptying and small intestinal transit, and ↑ lower oesophageal sphincter tone. Useful → ANTIEMETICS and in ➲ non-ulcer dyspepsia. Domperidone does not cross blood–brain barrier and has fewer side effects than metoclopramide, but no parenteral preparation.
- Erythromycin is a macrolide antibiotic with additional effects as a motilin agonist. Dose: 100mg PO/IV qds or 250mg PO/IV bd. Most effective single agent but long-term use limited by tachyphylaxis (develops over 2–7d). Enhances efficacy of dopamine antagonists.

Propranolol

GI indication	Prophylaxis against variceal bleeds in patients with ➔ portal hypertension.
Mode of action	Non-cardioselective β-blocker. Reduces portal pressure through ↓ in portal and collateral blood flow.
Dose/duration	40–80mg PO bd. Start at low dose and ↑ as systemic BP and HR allow.
Contraindication	Bradycardia, hypotension, 1st-degree heart block, asthma. Caution in heart failure as negative inotrope.
Side effects	Bradycardia, hypotension, depression, fatigue, impotence, nightmares, cold hands. Reduces warning signs of hypoglycaemia.
Practice points	Effective for primary and secondary prophylaxis (cheaper, safer, and easier than variceal band ligation, but compliance uncertain). Checking resting heart rate is a useful means of assessing drug response/compliance (aim for 25% ↓ in heart rate).

Proton pump inhibitors (PPIs)

(e.g. omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole).

GI indication	- ➔ Peptic ulceration. - ➔ *H. pylori* eradication, combined with antibiotics. - Useful in treating symptoms of gastro-oesophageal reflux, maintenance treatment of ulcerative or stricturing oesophagitis, and ➔ Barrett's oesophagus. - Prevention and treatment of NSAID-induced ulcers. - Treatment of hyperacidity in ➔ gastrinoma (➔ Zollinger–Ellison syndrome).
Mode of action	Irreversible blockade of H^+/K^+-ATPase system (the 'proton pump') of gastric parietal cell.
Dose/duration	- Omeprazole 20–40mg od. - Lansoprazole 15–30mg od. - Pantoprazole 40mg od, or for ▲ **acute upper gastrointestinal bleeding** ▲ 80mg IV bolus followed by 8mg/h infusion over 72h. - Rabeprazole 20mg/d.
Contraindication	No evidence of adverse safety in pregnancy, but omeprazole is the only PPI licensed in this population.

Side effects	- Drug interactions (particularly omeprazole):
	  - Alters metabolism of various antivirals and antifungals.
	  - ↓ Clearance of methotrexate, warfarin, diazepam, and phenytoin.
	  - May ↓ efficacy of clopidogrel through CYP450 inhibition (required to activate prodrug), though robust evidence of adverse outcomes lacking.
	- Predisposes to ➔ *C. difficile* infection.
	- Hypomagnesaemia.
	- ↓ Iron, and B_{12} absorption.
	- Interstitial nephritis.
	- Increased risk of osteoporosis and fracture, particularly with long-term use in elderly.
	- Mild-to-moderate long-term hypergastrinaemia suggested in recent study to predispose to gastric carcinoma, though potential confounders.
	- Some evidence ↑ risk of pneumonia, but debated.

Practice points	• Best given 15–30min before meals (70% of proton pumps secreting acid). Efficacy relatively limited if administered in fasting state (only 5% of proton pumps active). • 70% patients on bd PPI have nocturnal acid breakthrough (pH <4 for >1h); can be abolished in short term by adding → H_2 RECEPTOR ANTAGONIST. • Some evidence of dose response with high doses of omeprazole, which leads some to favour this PPI in difficult reflux or gastrinoma.

Ribavirin

GI indication	➔ Hepatitis C and E.
Mode of action	Guanosine analogue. No antiviral action given alone. Mechanism of benefit in combination with → INTERFERON ALFA uncertain.
Dose/duration	800–1200mg/d PO, with PEG-IFN.
Contraindication	Pregnancy, haemoglobinopathies (due to haemolysis, but use may be possible with careful monitoring), renal failure.
Side effects	Haemolysis (↓ in Hb to <100g/L in 14%), teratogenicity.
Practice points	• Ribavirin should not be given to ♀ patients during or within 4mo of planned pregnancy, and ♂ given ribavirin should use condoms during and for 6mo after treatment and if partner pregnant. • Much less used since direct-acting antivirals available.

Rifaximin

GI indication	• Recurrent ▲ **hepatic encephalopathy** ▲. • Small intestinal ➔ bacterial overgrowth.
Mode of action	Non-absorbable antibiotic. Binds bacterial polymerase and interferes with transcription.
Dose/duration	550mg BD PO, with or without lactulose.
Side effects	Nil.

Serotonin (5-HT$_3$) receptor antagonists

(e.g. ondansetron, granisetron).

GI indication	Severe nausea and vomiting.
Mode of action	Blocking of 5-HT$_3$ receptor-dependent afferent impulses to vomiting centre in medulla.
Dose/duration	• Ondansetron: e.g. 4–8mg PO/SC/IV tds. • Granisetron 2–9mg/d PO in divided doses.
Contraindication	Pregnancy/breastfeeding, severe liver impairment.
Side effects	Constipation, headache, abdominal discomfort, prolonged QT on ECG.
Practice points	Constipation induced by 5-HT$_3$ agonists may be severe, particularly in patients already on → OPIATES for pain.

Sofosbuvir

GI indication	➔ Hepatitis C.
Mode of action	NS5B polymerase inhibitor with pan-genotype action.
Dose/duration	400mg PO od for 12–24 wk.
Side effects	Very well tolerated. May cause headache and fatigue.
Practice points	Possible drug-drug interactions with rifampicin, carbamazepine, phenytoin, and St John's wort. Dose adjustments may be required in patients with renal impairment (eGFR<30).

Sucralfate

GI indication	➔ Gastritis; ➔ peptic ulceration; post-variceal sclero-therapy/banding ulcers; radiation proctitis (see ➔ radiation damage to the GI tract).
Mechanism	Complex of aluminium hydroxide and sulphated sucrose. Forms protective barrier against acid and other mucosal irritants.
Dose/duration	• Gastro-oesophageal disease: 1g PO qds. • Radiation proctitis: 2g PR qds, as enema.
Contraindications	Caution in renal failure.
Side effects	• May rarely cause gastric bezoars. • Binds some drugs, including phenytoin and warfarin.
Practice points	Separate administration from feed by >1h.

Tacrolimus

GI indication	• ➔ Liver transplantation. • Possible alternative to → CICLOSPORIN in ➔ ulcerative colitis.
Mode of action	Prevents T cell activation by inhibiting calcineurin pathway.
Dose/duration	Oral tacrolimus (Prograf®) bd (usual dose 0.1mg/kg/d, but doses vary based on maintaining trough blood levels at 5–10ng/mL). Advagraf® is once daily preparation.
Contraindication	Caution with concomitant antilymphocyte therapy, and in renal failure. Monitor K^+ and Mg^{2+}.
Side effects	• Neurological: tremor, headache, and paraesthesiae. • Nephrotoxicity. • Hypertension, hyperglycaemia, dyslipidaemia. • GI side effects: diarrhoea, abdominal pain, and nausea. Like ciclosporin, can cause eosinophilic colitis.
Practice points	Extensively metabolized via CYP450: concomitant inhibitors or inducers may affect blood levels.

Terlipressin

GI indication	• Acute variceal bleeding (see ▲ **acute upper GI bleeding** ▲ and ➲ portal hypertension): ↓ mortality. • Type 1 ➲ hepatorenal syndrome.
Mode of action	Longer-acting synthetic analogue of vasopressin. Peripheral and splanchnic vasoconstrictor: ↓ splanchnic blood flow and portal hypertension. ↑ Systemic vascular resistance may improve renal blood flow.
Dose/duration	1–2mg IV 4–6 hourly (slow peripheral injection).
Contraindication	Hypersensitivity; coronary artery disease; severe arrhythmias; myocardial infarction; stroke. Drug effect may be potentiated by carbamazepine and chlorpropamide.
Side effects	Vascular complications (e.g. myocardial infarction, arrhythmia, mesenteric/peripheral ischaemia, pulmonary oedema, stroke), vertigo, migraine, bronchoconstriction, abdominal cramps, nausea, and vomiting.
Practice points	Avoid if known coronary artery disease (check ECG prior to administration). Consider test dose of 0.5mg. If contraindicated, → OCTREOTIDE is an alternative.

Tofacitinib

GI indication	Moderate to severely active ➲ ulcerative colitis (in patients non-responsive/intolerant to conventional immunosuppressants or biologics).
Mode of action	Inhibits JAK and downstream inflammatory mediators.
Dose/duration	Usual dose 5mg PO bd. Trials show ↑ efficacy with 10mg bd, although more side effects (including infection).
Contraindication	Neutropaenia or lymphopaenia. Active infection.
Side effects	Abdominal pain, diarrhoea, hyperlipidaemia, herpes zoster, lymphoma, venous thromboembolism.
Practice points	Reduce dose to 5mg od if concurrent use of potent CYP450 inhibitors.

Ursodeoxycholic acid (UDCA)

GI indication	• ➔ Primary biliary cholangitis (PBC). • ➔ Obstetric cholestasis. • Biliary stone disease (see 'Practice points'). • Starting UDCA in new diagnosis of ➔ primary sclerosing cholangitis (PSC) is no longer recommended.
Mode of action	Displaces endogenous bile acids from enterohepatic circulation and stabilizes hepatocellular membranes. Promotes bile flow.
Dose/duration	• PBC: 12–16mg/kg/d in 3 divided doses for 3mo, then ↓ to 12–16mg/kg once daily at bedtime. • Gallstones: 8–12mg/kg nocte, to continue for 3–4mo after stones dissolve.
Contraindications	May ↓ absorption of aluminium-based antacids, colestyramine, and ➔ oral contraceptive pill.
Side effects	Fatigue, headache, rash, nausea, vomiting, dyspepsia, metallic taste, abdominal/biliary pain, diarrhoea, myalgia.
Practice points	Multiple meta-analyses suggest UDCA for treatment of PBC is associated with improvement in liver biochemistry, delayed disease progression, and possibly transplant-free survival. However, they do not confirm initial reports suggesting relief of fatigue and pruritus. Treatment appears more effective in patients with early disease. Patients with advanced PBC and complications of portal hypertension (e.g. ascites) do not benefit.

Ustekinumab

GI indication	Moderate-to-severe ➔ Crohn's disease or ➔ ulcerative colitis with inadequate or loss of response to conventional immunosuppressants and → ANTI-TNF drugs.
Mode of action	Monoclonal antibody against p40 subunit common to IL-12 and IL-23.
Dose/duration	Induction dose of 6 mg/kg IV, followed by 90mg SC after 8wk, then 90mg SC every 12wk.
Contraindication	Active infection. Screen for TB prior to treatment.
Side effects	Generally well-tolerated. Can get injection site reactions, infection, arthralgia, diarrhoea, headache, and myalgia.
Practice points	Recently approved in ulcerative colitis, and position in treatment pathway expected to evolve.

Vedolizumab

GI indication	Moderate-to-severe ➔ Crohn's disease or ➔ ulcerative colitis with inadequate or loss of response to conventional immunosuppressants and → ANTI-TNF drugs.
Mode of action	Monoclonal antibody against $\alpha_4\beta_7$ integrin, which blocks lymphocyte migration into GI tract.
Dose/duration	300mg IV, then further 300mg after 2wk, followed by 300mg after 4wk, then 300mg every 8wk.
Contraindication	Severe active infection.
Side effects	Generally well-tolerated, but can get injection site reactions and hypersensitivity. Unlike natalizumab, no confirmed cases of JC virus-related progressive multifocal leukoencephalopathy.
Practice points	• Induction of remission relatively slow with vedolizumab compared with steroids or anti-TNF, as does not eliminate activated lymphocytes already present in bowel but blocks further recruitment. • SC formulation in clinical trials.

Section 6

Emergencies

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Abdominal trauma

Abdominal trauma is divided into blunt and penetrating injuries, and may result in damage to viscera. Penetrating trauma usually obvious, but diagnosis of blunt trauma more likely to be delayed and can be missed altogether. Vehicular trauma is by far the most common cause, followed by physical assault, falls, and accidents during recreational activities. Rarer causes include iatrogenic injury during cardiopulmonary resuscitation or Heimlich manoeuvre. Abdominal organs and major vessels bleed profusely when cut or torn, and rupture of a hollow viscus carries major risk of peritonitis. The liver is the most vulnerable organ due to its size and location. Injury occurs more readily in children, as ribs more flexible (transmitting greater force) and developing viscera have weaker connective tissue frameworks.

Initial resuscitation

Patients with abdominal trauma have frequently been involved in high-risk injuries, and associated injures are common (thorax in 50%, bony pelvis in 20%). Initial resuscitation should proceed according to Advanced Trauma and Life Support (ATLS) guidelines, using the 'ABCDE' approach. Basic principles are to treat life-threatening problems first before moving on to next assessment, and reassessing from the beginning if any deterioration occurs.

- **Airway** Ask patient: 'Are you all right?' If no respiratory effort or palpable pulse, commence Basic Life Support. Stabilize C-spine (immobilization in semi-rigid collar often appropriate until can be formally assessed). Use jaw thrust to open airway if necessary. Remove visible foreign bodies (e.g. debris, blood) from mouth, consider simple adjuncts (e.g. oropharyngeal airway), and provide high-flow oxygen. Listen for stridor or gurgling.
- **Breathing** Look for respiratory distress (cyanosis, use of accessory muscles, abdominal breathing). Measure respiratory rate and SaO_2. Examine for pneumothorax, haemothorax, flail chest and pulmonary contusion; treat if present. Consider CXR and arterial blood gas.
- **Circulation** Assess peripheries (blue, pink, pale, or mottled; cool or warm). Measure capillary refill time (normally <2s), heart rate, and BP. Lie patient flat. Obtain secure IV access (2 large-bore 12–14G cannulae) and blood tests (FBC, U&E, LFT, amylase, coagulation screen, G&S/cross-match). Consider need for IV crystalloid infusion (initially 2L stat if hypovolaemic) ± blood products:
  - Haemorrhage is principal cause of preventable post-injury death. Assume hypotension due to blood loss until proven otherwise.
  - If patient has no (or only transient) response to IV crystalloid, give type-specific or O-negative blood (unless fully cross-matched units rapidly available), as shown to reduce mortality. Consider activation of ▲ **major haemorrhage protocol** ▲.

- **Disability** Assess conscious level using AVPU method (Alert, responds to Voice or Pain, Unresponsive). Common causes of unconsciousness are hypoxia, hypercapnia, head injury, hypoglycaemia, and drugs (including sedatives and analgesics). Examine pupils for size, equality, and reaction to light. Measure temperature and blood glucose. Place in recovery position if obtunded but C-spine secure.
- **Exposure** Reveals other areas of trauma and enables procedures such as Focused Assessment with Sonography for Trauma (FAST) scan or diagnostic peritoneal lavage (DPL); see p. 653. Loosen/remove clothes as necessary, but aim to respect dignity and minimize heat loss as far as possible.
- **AMPLE history** Allergies, Medications, Prior illnesses/operations, Last meal, Events, and environment surrounding injury.
- Ongoing management depends on haemodynamic stability, defined as SBP >90mmHg and HR <100/min following these measures.

r Pitfall. Concealed haemorrhage

Large volumes of blood can accumulate in peritoneal or pelvic cavities with minimal clinical signs. Many injuries not visible/missed on initial survey, and examination notoriously unreliable in this setting. Missed intra-abdominal injuries and concealed haemorrhage are frequent causes of morbidity and mortality. Beware distraction by other injuries or intoxication. Frequent serial examinations required.

Haemodynamically unstable

Patients should have a FAST scan (or DPL if this is unavailable) with aim of detecting intraperitoneal haemorrhage (see p. 653). If positive, immediate emergency laparotomy indicated to control bleeding. If negative, investigation should proceed to CT. FAST scan also used to exclude haemothorax and haemopericardium.

Borderline haemodynamic stability

Patients with transient responses to fluid resuscitation require urgent contrast CT to detect and quantify haemoperitoneum, active haemorrhage, vascular disruption, and visceral injury. Extraluminal contrast and intraparenchymal blush are neither completely sensitive nor specific for ongoing haemorrhage, but should be taken seriously as predict need for angiographic embolization or laparotomy. Pneumoperitoneum suggests rupture of hollow viscus.

Haemodynamically stable

Most (≈85%) of patients with abdominal injury will be stable or only mildly hypotensive, and can be managed conservatively. If GCS 15/15, no abdominal pain or tenderness and no distracting injuries, can be observed in emergency department then discharged. Presence of any of these features mandates abdominal CT and admission for minimum of 24h observation. Additionally, any patient attending following high-risk injury (e.g. death of another passenger in same vehicle in road traffic accident) should be observed for 24h. Any deterioration should prompt repeat imaging ± laparotomy.

Blunt trauma

Three mechanisms of injury seen:

- **Deceleration** Causes differential movement of structures, resulting in shear. Classic injuries are hepatic tears along ligamentum teres, intimal injury to renal arteries, and splanchnic vessel damage.
- **Crush** Between anterior abdominal wall and vertebral column. Liver, spleen, and kidneys particularly vulnerable.
- **External compression** Commonly by seat belt, steering wheel, or bicycle handlebar. Cause hollow viscus or pancreatic rupture.

History

Ascertain whether following present (predict significant organ injury):

- Extensive vehicular damage.
- Prolonged extrication required.
- Passenger side intruded, or passenger death.
- Patient ejected from vehicle.
- Use of seatbelt (↓ incidence of head and thoracic injury, but ↑ pancreatic and intestinal injury).
- Deployment of air bag.
- Alcohol or drug use.
- Head or spinal injury.
- Out-of-hospital hypotension.

Examination

- Seat belt marks: 30% risk of visceral injury, especially small intestinal rupture.
- Steering wheel or bicycle handlebar-shaped contusions.
- Abdominal distension.
- Flank (Grey-Turner sign) or peri-umbilical (Cullen sign) ecchymoses: suggest retroperitoneal haemorrhage.
- Peritonism.
- Rib fracture: risk of liver or splenic injury.
- Bowel sounds in thorax: may indicate diaphragmatic injury.
- Digital rectal examination: blood can suggest bowel injury. In ♂, high riding prostate may indicate genitourinary injury.
- Urethral meatus: blood suggests injury to pelvic organs.

Penetrating trauma

Penetrating injuries tend to be more obvious than blunt trauma, and physical examination more reliable. Close range injuries transfer greater kinetic energy than distant ones. Gunshots involve high energy ∴ pattern of injury difficult to anticipate, and secondary missiles (bullet or bone fragments) cause additional damage. Stab wounds much more predictable. Impaling objects may tamponade bleeding, so do not remove unless definitive treatment can be provided. Diagnostic laparoscopy may be helpful.

Bedside procedures

FAST scan

Focused bedside US has now largely replaced DPL, with superior diagnostic accuracy. Four acoustic windows examined: peri-cardiac, peri-hepatic, peri-splenic, and pelvic. Scan positive if free fluid demonstrated, but otherwise deemed indeterminate if any window cannot be visualized.

Diagnostic peritoneal lavage (DPL)

Historically used to determine which patients needed exploratory laparotomy, but now should be relegated to scenarios whether FAST not available. Performed by introducing catheter into peritoneal space to sample fluid. Positive if can aspirate ≥10ml bloody fluid prior to introduction of lavage infusate, or if siphoned lavage contains ≥10^5 RBCs or ≥500 WBCs/μl. Sensitivity for haemoperitoneum 98–100% and specificity 90–96%. Also send sample for amylase measurement, as ↑ may indicate pancreatic rupture. Complications: bleeding from incision and catheter insertion, injury to intra-abdominal structures. Limitations include significant false-positive frequency (resulting in 25–36% non-therapeutic laparotomy rate), inability to use for serial assessments, and difficulty performing in pregnant women.

Specific situations

Hepatic trauma

Most common mechanisms of injury are deceleration and direct blows to the abdomen, disrupting liver capsule and parenchyma at diaphragmatic attachments. Shear forces propagate along hepatic venous branches. Penetrating injuries may lacerate parenchyma but leave capsule intact. Contusion may result from compression against ribs or spine. Injuries to the gallbladder or bile ducts are rare.

Contrast CT defines the nature and severity of liver injury, and identifies complications (Liver Injury Scale 🖱 http://www.trauma.org/archive/scores/ois-liver.html most widely used classification, but does not emphasize arterial bleeds that may be amenable to angiographic embolization). Best indicators of need for surgery are haemodynamic instability, active extravasation, or sentinel clot (high attenuation at site of bleeding). Major hepatic vein injury must be known to surgeon prior to laparotomy, as mobilization of liver predisposes to massive haemorrhage.

Most patients are best managed non-operatively (in the absence of haemodynamically instability, peritonism, and high-grade injuries on CT). Most of those with defined injuries and borderline haemodynamic instability can be managed using arterial embolization. Those with large volumes of intra-abdominal fluid or active hepatic haemorrhage require surgical haemostasis. Hepatectomy, or vascular isolation or shunting, are reserved for advanced injuries, as high associated mortality. After surgery, further CT should be performed to identify any continuing haemorrhage, which may be amenable to embolization.

Complications include delayed haemorrhage (3.5%; <20% require transfusion), haematoma, infarction (due to disrupted blood supply), bile duct injury (biloma in 3%, leakage, fistulation, haemobilia, biliary peritonitis), and abdominal compartment syndrome. Haematomas may be asymptomatic but should usually be embolized due to risk of rupture. Distal bile leakage is typically transient without clinical significance, but proximal leaks can cause abscess or peritonitis (develop slowly over weeks); management is conservative, or with ERCP, percutaneous stenting, or surgery depending on severity. Late complications include abscess formation and ➲ biliary strictures. Overall mortality 10%, although only 2% attributable to liver injury (remainder due to associated head injuries or sepsis).

Splenic trauma

Up to 45% of patients with blunt abdominal trauma will have splenic injury. Susceptible following impact to left upper abdomen or lower thorax. Lower rib fracture ↑ risk. CT gold standard for diagnosis. Low-grade injuries in haemodynamically stable patient may be managed non-operatively, but most other patients require urgent surgical exploration ± splenectomy. Angioembolisation can reduce need for splenectomy; complications include splenic infarction and abscess formation.[1] Post-operatively, vaccinate after >2wk against pneumococcus, *H. influenzae* and meningococcus, and against influenza annually. Provide lifelong antibiotic prophylaxis with penicillin V 250mg PO bd (erythromycin 250mg PO bd if allergic).

Pancreatic trauma

Accounts for 4% of intra-abdominal injuries. In areas of high violent crime, penetrating trauma accounts for ~70%; otherwise compression injuries (e.g. bicycle handlebars) and deceleration-induced crushes against L1/L2 vertebrae responsible for most of the remainder. As the pancreas is closely associated with vasculature, there is significant morbidity and mortality. Serum amylase is an unreliable marker of tissue damage. CT is the initial imaging modality of choice, although 20–40% of injuries are missed if performed within 12h of trauma due to surrounding oedema, obscured pancreatic fracture planes, and closely opposed segments; repeat if initial scan negative but likelihood of significant injury is high. CT also poor at delineating ductal injury, hence MRCP, ERCP, or operative pancreatography if suspected.

Low-grade pancreatic injuries are usually managed with drainage and local debridement. Medium grade require distal pancreatectomy ± splenectomy, and high-grade need complex resections ± duodenectomy.[2] Post-operatively, patients may require treatment of pancreatic endocrine and exocrine insufficiency. Up to 20% develop pancreatic fistulae, although these often settle with conservative management.

Pregnant patients

Abdominal trauma in pregnant women carries high risk of foetal mortality, through direct injury or premature delivery. Standard care prioritizes stabilization of gravid woman over foetus. However, consider peri-mortem caesarean section in an otherwise unsalvageable situation.

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[1] Hildebrand DR *et al.* (2014). *BMJ* **348**: g1864.

[2] Lahiri R *et al.* (2013). *Ann R Coll Surg Engl* **95**: 241–5.

Acute abdominal pain

Acute abdominal pain is a common casualty presentation ('the acute abdomen') and reason for patients to require review on the ward. The duration of pain that defines it as acute is ill-defined, but usually no more than a few days. A huge range of GI and non-GI causes of abdominal pain may present acutely (Box 6.1). The challenge is making a differential diagnosis based upon history and examination, allowing investigations to be targeted to the specific clinical setting.

Clinical assessment

- Ask about the following aspects of the pain:
  - **Site** Particular intra-abdominal organs and diseases tend to produce pain localized to classic abdominal segments (see Fig. 1.3 and ► Approach to chronic or recurrent abdominal pain).
  - **Character** Colic tends to wax and wane in a regular manner due to spasm of muscular viscus (gallbladder, ureter, bowel), and the patient cannot find a comfortable position during attacks. In peritonitis, pain is constant and unremitting, and the patient wishes to lie still. Pain arising from abdominal viscera tends to be largely midline, dull, and poorly localized. Inflammation of parietal peritoneum is sharper, well localized, and exacerbated by movement. Small bowel pain localizes to umbilicus, while large bowel pain is usually felt in the lower abdomen.
  - **Onset, severity, and duration.**
  - **Radiation** Right shoulder tip in ➲ cholecystitis; to the back in ➲ acute pancreatitis.
  - **Relieving and exacerbating factors.** Ask about relationship to oral intake and bowel movements.
- Ask about associated symptoms:
  - Vomiting, diarrhoea, nature of stool, and abdominal distension.
  - Faeculent vomiting and absolute constipation suggest distal intestinal/colonic obstruction.
  - In small bowel obstruction, vomit often bilious and large volume.
- Take a full genitourinary and gynaecological history.
- Have there been previous episodes, and has a diagnosis been made? Any previous surgery (e.g. adhesions, ➲ Crohn's disease)?
- Do other medical problems hint at diagnosis (e.g. arteriopathy with AF and acute abdominal pain may suggest ➲ intestinal ischaemia), flare of ➲ erythema nodosum in inflammatory bowel disease.
- Full **examination is** essential, including assessment for evidence of hypovolaemia or shock. See ▷ Gastrointestinal examination, p. 130. In generalized peritonitis there may be rigidity, guarding and rebound tenderness (although these can be masked in patients on high-dose steroids). Complete examination should include inguinal and supraclavicular lymph nodes, hernial orifices, femoral pulses, external genitalia (testicular torsion may be experienced as central abdominal pain), bowel sounds (may be absent in peritonitis/ileus, tympanic in obstruction), bruits, and rectal examination.

Box 6.1 Causes of acute abdominal pain

Note: some conditions can present recurrently!

Generalized parietal pain due to peritonitis

- Perforated viscus (e.g. ➲ peptic ulceration, ➲ diverticulitis).
- Bacterial peritonitis (and ➲ spontaneous bacterial peritonitis).
- Ruptured intra-abdominal cyst.
- ➲ Familial Mediterranean fever.

Localized peritoneal pain

- ➲ Appendicitis, ➲ cholecystitis, regional enteritis, colitis, abdominal abscess, ➲ acute pancreatitis, hepatitis, lymphadenitis, endometriosis, ➲ diverticulitis.

Pain from increased tension in viscera

- ▲ **Bowel obstruction** ▲.
- Intestinal hypermotility.
- Biliary (➲ choledocholithiasis) or ureteric obstruction.
- Hepatic capsule distension (e.g. ➲ liver abscess, ➲ hepatocellular carcinoma, liver metastasis, large liver cysts).
- Renal capsule distension.
- Ectopic pregnancy.
- Abdominal aortic aneurysm.
- Severe constipation.

Ischaemia

- ➲ Intestinal ischaemia (arterial stenosis, embolism).
- Splenic infarction, hepatic infarction.
- Torsion (gallbladder, cyst, omentum, ➲ volvulus, appendix, testes).
- Tissue necrosis.
- Sickle cell crisis.

Retroperitoneal causes

- Tumours (e.g. ➲ pancreatic cancer).
- Retroperitoneal abscess.
- ➲ Acute/chronic pancreatitis.

Extra-abdominal

- Thoracic (basal pneumonia, pulmonary embolus, inferior myocardial infarction, ➲ oesophagitis).
- Neurological (neurogenic tumours, spinal disease, herpes zoster).
- Metabolic (diabetic ketoacidosis, hypercalcaemia, Addisonian crisis, acute intermittent ➲ porphyria, uraemia).
- Vasculitis, including ➲ Henoch–Schönlein purpura.
- Poisoning (e.g. lead).

Functional

- ➲ Irritable bowel syndrome.
- Flares of chronic pain syndromes, opioid withdrawal.

Investigations

Specific investigations are tailored to the differential diagnosis arising from initial assessment, but in most cases will include:

- Blood tests:
  - FBC, U&Es, glucose.
  - LFTs. ALT >1,000IU/L usually due to drugs (e.g. paracetamol), acute viral ➲ hepatitis, or hepatic ischaemia.
  - Coagulation screen. May be abnormal in severe sepsis or chronic liver disease, and will be required prior to surgical intervention.
  - Amylase. Elevated in many causes of abdominal pain; only indicative of ➲ acute pancreatitis if >5× ULN + consistent history. May be normal in ➲ chronic pancreatitis.
  - ESR/CRP. If significantly ↑ suggests inflammation/infection. CRP of prognostic value in ➲ acute pancreatitis.
  - Albumin ↓ in chronic liver disease, as well as during acute phase response (hence seen with many other causes of severe illness, such as ➲ acute pancreatitis).
  - Venous blood gas. ↑ lactate (may indicate organ hypoperfusion), metabolic acidosis.
  - Blood cultures.
  - G&S if laparotomy or transfusion requirement possible.
- Urine β-HCG pregnancy test in all women of childbearing potential (ectopic pregnancy?). Serum can be requested if patient anuric.
- Urinalysis (± MSU for MC&S if infection suspected).
- ECG.
- Erect CXR. Air under diaphragm due to viscus perforation.
- Supine AXR (often non-contributory, but may show bowel dilatation (>2.5cm small bowel, >6cm colon) and air–fluid levels in obstruction, or faecal loading exacerbating ➲ ulcerative colitis.
- Abdominal US. Useful for exclusion of acute cholecystitis and biliary obstruction; detection of abdominal fluid and collections; and assessment of organomegaly, masses, and aortic aneurysms. Helpful in ➲ acute pancreatitis to identify underlying gallstone disease.
- Abdominal CT. More sensitive than US in most circumstances (except ➲ gallstones). Allows much better views of pancreas and retroperitoneum. CT angiography if vascular cause suspected.
- Diagnostic laparoscopy may have role in investigation of acute abdominal pain associated with ▲ **abdominal trauma** ▲, or in women with unexplained RIF pain. Contraindicated in peritonitis, obstruction, or intra-abdominal adhesions.

Management

A clear diagnosis may not possible on the basis of initial assessment and investigations. Specific treatment is largely determined by differential diagnosis (see A–Z section according to diagnoses) and the process underlying acute abdominal pain.

- If evidence of peritonitis, viscus perforation, or obstruction, urgent surgical involvement is required.
- If laparotomy may be required, ensure blood available, and CXR/ECG performed beforehand with appropriate anaesthetic risk assessment.
- Keep NBM.

- Obtain IV access and resuscitate with crystalloid/blood according to degree of hypovolaemia and blood loss. If shocked, give IV fluid challenge (250–500ml 0.9% saline or Hartmann's solution stat) and monitor response (HR, BP, urine output). Repeat as necessary.
- Pass NG tube if evidence of obstruction; keep on free drainage and ensure all output measured.
- Insert urinary catheter and monitor hourly output.
- If infection suspected, prescribe antibiotics according to local hospital policy and possible cause of infection.
- Pain of peritonitis may be severe, and analgesia should not be withheld for fear of 'masking' clinical features. Opiates (start with morphine 2.5–5mg IV or more, if not opiate naïve). Give with → ANTIEMETIC: metoclopramide 10mg IV/IM (though avoid in possible mechanical obstruction), cyclizine 50mg IV/IM, or ondansetron 4-8mg IV.
- Laparotomy usually indicated for generalized peritonitis related to viscus perforation (e.g. duodenal ulcer) or following organ rupture.

Where a definitive diagnosis cannot be made, a fundamental aspect of management is regular review and reassessment of the clinical course and of response to initial treatment.

Acute diarrhoea

Diarrhoea can constitute an emergency if associated with severe disturbances in fluid or electrolyte balance, an invasive pathogen, or toxic dilatation of the colon.

Acute watery diarrhoea

Usually infectious (see ► Approach to acute diarrhoea).

Common causes:

- Viruses. ➲ Rotavirus in infants and young children can cause profound dehydration. Illness lasts ~7d (➲ adenovirus longer).
- In adults, enterotoxigenic ➲ *Escherichia coli* (ETEC).
- Food-borne pathogens (see ➲ food poisoning):
  - Bacteria that colonize gut: ➲ *Salmonella*, ➲ *Campylobacter*, enterohaemorrhagic ➲ *Escherichia coli*, *Vibrio* spp. (*V. parahaemolyticus, V. cholerae*), ➲ *Yersinia*, ➲ *Clostridium perfringens*.
  - Pre-formed toxins: *Staphylococcus aureus* (NB: symptoms include nausea, vomiting, and abdominal cramps, but less commonly diarrhoea), *Bacillus cereus, Clostridium botulinum*.
- Invasive pathogens and protozoa can produce watery diarrhoea in initial stages.
- Spectrum of pathogens differs in immunocompromised patients (e.g. HIV-infected). Consider ➲ coccidia (*Cryptosporidium*, *Microsporidium*), viral (CMV), and neoplastic (➲ lymphoma, ➲ Kaposi's sarcoma) causes.

Diarrhoea with blood

Making diagnosis is important because of need to differentiate infection from inflammatory bowel disease and other disorders. Differential diagnoses include:

- Invasive infectious diarrhoea (dysentery): ➲ *Shigella*, ➲ *Salmonella*, ➲ *Campylobacter*, EHEC, and ➲ amoebiasis.
- ➲ Ulcerative colitis, ➲ Crohn's disease.
- ➲ Ischaemic colitis.
- ➲ Radiation colitis.
- ➲ Colorectal cancer.
- ➲ Diverticular disease.
- ➲ Intussusception.

Toxic dilatation

Colonic dilatation (transverse colon diameter >6cm or caecum >10cm on plain AXR). Worrisome for perforation risk. Occurs in:

- Severe ➲ ulcerative colitis or colonic ➲ Crohn's disease.
- Infectious colitis.
- Acute distal obstruction (➲ volvulus or carcinoma).
- Acute pseudo-obstruction (see ➲ Ogilvie's syndrome).

Making a diagnosis

Clinical examination

May not yield diagnosis but important to estimate **dehydration.** Textbooks always say look for dry tongue, loss of skin turgor, and tachycardia, but these are unreliable. Best signs are **postural drop in BP** or **postural tachycardia**. Look also for signs of inflammatory bowel disease (see ▷ Gastrointestinal examination, p. 130) or immune compromise (oral candidiasis, ➲ Kaposi's sarcoma, oral hairy leukoplakia, retinitis, generalized lymphadenopathy). Toxic dilated colon usually accompanied by fever, tachycardia, abdominal distension, and neutrophilia. Fever and peritoneal signs may indicate infection with invasive pathogen.

Investigations

Blood tests

- Significant volume depletion may be indicated by haemoconcentration (↑ Hb, ↑ packed cell volume, ↑ urea), acute kidney injury, or metabolic acidosis (↓ pH, ↓ bicarbonate, base deficit, ↑ lactate).
- Inflammatory markers (CRP, ESR) may be raised but non-specific.
- Potassium and magnesium losses can become significant.
- Eosinophilia accompanies helminthic infections, although only ➲ *Strongyloides*, *Trichinella*, and ➲ schistosomiasis associated with diarrhoea (see ➲ eosinophilia and the GI tract).

Microbiological examination of the stool

Distinguishing infection from inflammatory bowel disease is important, but microbiological results take at least 1–2d (and often longer for slow-growing organisms).

- Stool MC&S and *Clostridioides difficile* assay (see ➲ Clostridial infections of the GI tract).
- Blood cultures if patient febrile, dysenteric, or systemically unwell.
- Faecal antigen ELISAs available for ➲ *Giardia* and ➲ rotavirus.
- DNA probes often do not work on crude faecal extracts but can help in characterizing bacterial isolates.
- Antimicrobial chemotherapy indicated for dysenteric infections such as ➲ amoebiasis, ➲ shigella, and *C. difficile* (see ► Approach to acute diarrhoea).

Radiological imaging

- Main use of plain AXR is to detect toxic megacolon. However, gas-filled colon devoid of faeces suggests pancolitis, and loss of haustration and dilatation indicate severe inflammation. May be multiple small bowel fluid levels and dilatation (indicating partial ileus rather than complete obstruction).
- Abdominal US can show bowel wall thickening and adenopathy.

Endoscopy

Sigmoidoscopy can be highly informative, demonstrate colitis, and allow biopsy (which may help differentiate infection from inflammation). Appearances of amoebic colitis, ischaemic colitis, radiation colitis, and pseudomembranous colitis can be diagnostic. Full **colonoscopy** usually not necessary and may be risky.

Management

Fluid replacement

- Most cases of acute infective diarrhoea are self-limiting, provided attention paid to restoring fluid balance.
- Oral rehydration is the mainstay of managing acute watery diarrhoea (see ➲ oral rehydration solutions).
  - WHO oral rehydration solution (sodium concentration 90mM, osmolality 331mOsm/kg) recommended for those with severe diarrhoea (provides adequate glucose for sodium–glucose co-transporter), or those with short bowel or jejunostomy.
  - In children with acute diarrhoea, recommendation is for oral rehydration solution with lower sodium concentration (~50mM) (see ▶ Approach to acute diarrhoea).
- Reserve IV fluids for those with haemodynamic compromise (tachycardia, hypotension, oliguria), severe electrolyte disturbance (particularly hypokalaemia), or for when oral route unavailable (e.g. intractable vomiting).
- If patient does not have signs of invasive pathogens, loperamide may be considered.

Antibiotic therapy

- Most patients with acute watery diarrhoea do not require antibiotics. However, consider empiric treatment in:
  - Patients with moderate or severe diarrhoea and signs suggestive of invasive bacterial pathogen (fever, peritonism, bloody diarrhoea).
  - The elderly.
  - Immunocompromised patients.
- Usual empirical therapy is with oral fluoroquinolone (e.g. ciprofloxacin 500mg bd) for 3d or azithromycin 1g single dose. Exceptions include:
  - Suspected ➲ *Campylobacter* infection or traveller's diarrhoea following visit to Indian subcontinent. High rates of resistance, so use azithromycin 500mg PO od for 3d.

  - Pregnant or breastfeeding women, and children. Causes musculoskeletal adverse effects.
- Once pathogen identified, switch to targeted antibiotic therapy.
- Treatment for patients with suspected or proven enterohaemorrhagic *E. coli* (EHEC) primarily supportive. Antibiotics not recommended due to ↑ risk of haemolytic–uraemic syndrome.

Common mistakes and important points in early management

- Always think of **toxic megacolon.** If abdominal tenderness and signs of systemic upset, get plain AXR.
- If patient unwell, **frequent review** by senior clinician essential, as is **surgical opinion**.
- IV fluids: keep **potassium** >4.0mmol/L.
- Do not assume that acute diarrhoea (even if bloody) in patient with known inflammatory bowel disease is due to flare of disease. Infection will be cause in ~15% of cases.
- Monitor FBC and electrolytes daily.
- If colon dilated, monitor diameter on daily X-rays.
- Stop any drugs that may contribute to colonic paralysis, especially opiates and antidiarrhoeal agents.
- **Avoid NSAIDs**. Can aggravate diarrhoea and profoundly reduce renal cortical blood flow, precipitating acute kidney injury in hypovolaemia or patients with pre-existing kidney disease.
- In fulminant colitis or toxic dilatation of the colon, decision to proceed to colectomy can be difficult. Useful indicators are:
  - Increasing tachycardia and fever.
  - Failure to improve clinically or radiologically (i.e. colon diameter decreasing) after 24h.
  - Signs of perforation (can be minimal, and masked by steroid use).
  - Mucosal islands seen on X-ray.

Complications

Worldwide, majority of deaths result from dehydration and acidosis. Complications of infection, especially by invasive pathogens, include:

- ➔ Haemolytic–uraemic syndrome.
- ➔ Septic arthritis.
- ➔ Reactive arthritis.
- Guillain–Barré syndrome.

Acute liver failure

Definition

Acute liver failure (ALF) characterized by sudden loss of hepatic function resulting in ▲ **hepatic encephalopathy (HE)** ▲, jaundice, and coagulopathy. Divided into three groups according to development of HE: hyperacute (0–7d), acute (1–4wk), and subacute (4–12wk).

Aetiology

- Differs markedly according to geography.
- Drug-induced causes most common in West: paracetamol in 45%, idiosyncratic drug reaction in 15%.
- ➲ Viral hepatitis most common cause worldwide.
- Uncertain cause in 15%, but 20% of these may relate to undiagnosed ➲ paracetamol overdose.
- See Table 6.1 for initial investigations.

Clinical syndrome

ALF is a systemic condition, characterized by:

- **Cardiovascular**. Intravascular volume depletion common. Clinical features similar to septic shock (↓ BP, peripheral vasodilatation, hyperdynamic circulation, tachycardia, ↓ systemic vascular resistance, ↑ cardiac output). Central venous and arterial catheters required to assess volume status. Inotropes (noradrenaline) commonly required.
- **Respiratory**. Intubation required in patients with GCS<8 or severe agitation/confusion. Acute lung injury can occur.
- **Neurological**. Neurological dysfunction common, with rapid onset. Patients with grade 1 HE should be transferred to transplant centre. Young patients (<35y) with high-grade HE (>3) and plasma ammonia >150µmol/L at risk of cerebral oedema. Seizures are a poor prognostic sign. Intracranial monitoring may be required.
- **Renal and metabolic**. Renal dysfunction in >50%. Volume resuscitate. Start renal replacement early if needed. Hypoglycaemia common and tight glucose control (6–10mmol/L) necessary.
- **Gastrointestinal**. Nutritional support required. Pancreatitis should be excluded as may preclude liver transplantation.
- **Infection**. Perform septic screen in all patients. Prophylactic antibiotics and antifungals needed due to ↑ rates of bacterial (>80%) and fungal infections.
- **Haematology**. ↑ INR, ↓ platelets, ↓ fibrinogen. Correct coagulopathy only if significant bleeding.

Table 6.1 Investigations for ALF

Haematology	FBC
	Blood film
	Clotting studies
	Haemolysis screen*
	Thrombophilia screen*
	Bone marrow aspirate and trephine*
Biochemistry	U&Es
	LFTs
	Arterial blood gas and lactate
	Paracetamol and salicylate levels
	Copper studies*
	Urate*
Immunology	Autoantibodies
	Immunoglobulins
Serology	HAV IgM
	HBsAg, HBsAb, HB IgM core Ab, HBV DNA
	HCV Ab, HCV RNA
	HEV IgM and viral load
	HSV IgM and viral load
	CMV IgM and viral load
	Leptospira IgM
Imaging	Doppler liver US
	CT with contrast

*When clinically indicated

Making the diagnosis

- ALF is a clinical diagnosis, based on demonstrating ▲ **hepatic encephalopathy** ▲ in patient with acute liver disease. ↑ Bilirubin and ↑ PT are the best blood markers of significant liver disease. See also ▶ Approach to recent-onset jaundice.
- Differentiating ALF from first presentation of acute-on-chronic liver disease may be difficult, but important as management, and prognosis, are very different. Is there any history suggesting chronic disease (speak to GP/review hospital notes/check historical blood results)? Are there signs of chronic liver disease (see ⊳ 'GI examination', p. 130)? Evidence of ➔ portal hypertension (splenomegaly, dilated superficial veins) unusual in ALF but can occur in subacute failure.

Finding the cause (see Table 6.2)

- May be obvious, but information from patient, relatives, and medical attendants vital, including: drugs (prescribed/recreational/herbal), risks for viral hepatitis, autoimmune diseases (e.g. thyroid/rheumatoid arthritis). Any evidence of hypotensive episode (recent surgery/ ↓ BP on observation chart/bleed/adverse cardiac event)? Any history of thrombosis or pro-thrombotic tendency (e.g. antiphospholipid syndrome), precipitating ➲ Budd–Chiari syndrome?

- Extent of investigation dependent on clinical scenario (e.g. low yield on leptospira serology in 80-year-old with ALF following prolonged cardiac arrest!).

Table 6.2 Causes of acute liver failure

Cause	Diagnosis in ALF	Comments
➲ Hepatitis A	Anti-HAV IgM	Possible ↑ rate of ALF if also chronic HCV
➲ Hepatitis B	IgM Anti-HB core (HBsAg may be –ve in ALF)	ALF in 1% of acute infections, especially if co-infection with HDV
➲ Hepatitis C	HCV RNA (Ab often –ve)	Rarely causes ALF
➲ Hepatitis E	Anti-HEV IgM and viral load	ALF in 20% of ♀ infected during pregnancy in South Asia/Indian subcontinent
Other infection (e.g. EBV, HSV, ➲ leptospirosis)	PCR for HSV and EBV; ELISA and PCR for leptospirosis, with organism found in urine after 7–10d	See ➲ leptospirosis
➲ Paracetamol overdose	Blood levels	Most common cause of ALF in UK
Drug reactions: e.g. NSAIDs, isoniazid, herbal remedies	Drug history, eosinophils Blood/urine analysis	See ➲ drug-induced liver injury
Toxins (e.g. *Amanita phalloides* mushrooms)	History of ingestion	
➲ Acute fatty liver of pregnancy	History, bloods, US	Mainly clinical diagnosis. See entry in A–Z. Especially 3rd trimester
➲ HELLP syndrome	History, bloods	Mainly clinical diagnosis. See entry in A–Z. Occurs in 2nd and 3rd trimester
➲ Wilson's disease	Urinary copper, caeruloplasmin	Usually presents with ALF <20 years of age
Hepatic ischaemia	↑ AST/ALT (>1,000U/L), CT, ECG for arrhythmia	Especially following episode of hypotension
➲ Budd–Chiari syndrome	US, history for risk factors	May present with ascites
➲ Autoimmune hepatitis	AutoAbs, Igs	
Malignant infiltration	Imaging, histology	
'Seronegative hepatitis'	All above excluded	~15% of cases

Management

Optimal management depends on general supportive measures, consideration of specific treatments, prognostic assessment, and need for ➲ liver transplantation.

General approach

- Manage in HDU/ITU setting.
- Pass urinary catheter and monitor hourly urine output.
- Monitor vital signs (HR/BP/temp) every 30min to 2h.
- Daily bloods for FBC, U&E, bicarbonate, glucose, clotting, LFTs.
- CXR, and culture blood, urine, and sputum, even if afebrile.
- Meticulous care of catheters/lines, and strict aseptic insertion.
- Investigate cause of ALF as directed by history (see 'Finding the cause', p. 665 and Table 6.2). Note that paracetamol levels may be apparently subtoxic/undetectable by time of development of ALF. ↑↑ ALT/AST >1,000U/L most likely due to hepatic ischaemia, acute viral hepatitis, or drugs.
- Discuss with specialist liver transplant unit **early**. Detailed referral criteria vary according to cause and type of ALF, but broadly include any of: PT >30s; HE; creatinine >200µmol/L; hypoglycaemia; metabolic acidosis (pH <7.3). If in doubt, ask. Every unit prefers an unnecessary to a late call.
- Avoid all potentially hepatotoxic drugs (e.g. NSAIDs) and those that worsen complications of ALF (e.g. ACE inhibitors, opiates).
- Maintain nutrition, as ALF is catabolic state. NG feeding preferable as may prevent bacterial translocation, but ileus can preclude this.
- Central venous and arterial monitoring usually required to guide fluid management.
- Ensure adequate intravascular filling with crystalloid or blood products. If mean arterial pressure (MAP) <60mmHg despite filling, consider noradrenaline, but specialist inotrope management will be required.
- Monitor blood glucose. Give 10–20% glucose infusions if hypoglycaemic.
- → ACETYLCYSTEINE should be considered in all patients with ALF, as early use may prevent progression to severe encephalopathy, even when ALF not paracetamol-induced. Optimum dosing regimen not established, but most protocols used are similar to those employed for ➲ paracetamol overdose.
- ➲ Vitamin K 10mg/d IV for 3d (but usually has no effect on PT, unless vitamin K deficiency related to prolonged biliary obstruction). PT/INR very useful markers of clinical course/prognosis, so only give fresh frozen plasma or specific clotting factors (e.g. recombinant factor VIIa) if actively bleeding or require invasive procedure. Discuss use prior to administration with transplant centre.
- Maintain platelet count $>20 \times 10^9$/L with infusions.
- Acid suppression ↓ risk of haemorrhagic gastritis. Usually give oral/NG → PROTON PUMP INHIBITOR (e.g. omeprazole 20mg od), although clear evidence relates to IV → H_2 RECEPTOR ANTAGONISTS.

- No definitive role for prophylactic antibiotics, but often given. Low threshold for broad-spectrum IV antibiotics (e.g. 3rd-generation cephalosporin, or piperacillin-tazobactam) if any sign of sepsis. Prophylactic fluconazole and liposomal amphotericin ↓ risk of systemic fungal infection.
- Specific treatments may be required depending on aetiology:
  - In ALF due to mushroom poisoning, consider penicillin G and silymarin, but liver transplantation usually necessary.
  - ALF due to herpesvirus or zoster should be treated with → ACICLOVIR.
  - ➲ Autoimmune hepatitis treated with high-dose corticosteroids.
  - For ➲ acute fatty liver of pregnancy or ➲ HELLP syndrome, expeditious delivery recommended.

Specific management

Cerebral oedema/hepatic encephalopathy

- Intracranial hypertension accounts for 20% of ALF deaths.
- Avoid stimulation, and sedation, if possible.
- Lactulose in early stages of encephalopathy.
- Elevate head of bed to 30°.
- Consider CT brain to exclude cerebral bleed.
- 20% mannitol 0.5g/kg IV bolus, repeated as necessary (but not if serum osmolality >320mOsm/L).
- Low threshold for intubation/mechanical ventilation in view of risk of aspiration and agitation in patients with cerebral oedema and ≥grade III encephalopathy.
- Control seizures with phenytoin and low-dose benzodiazepines.
- Controlled hyperventilation may help contain surges of raised intracranial pressure (ICP) in patients unresponsive to mannitol.
- In specialist unit, ICP monitor may be inserted in comatose patient to measure degree of cerebral oedema accurately (but risk–benefit of such monitoring much debated). Transcranial Doppler may also be helpful.
- Therapeutic hypothermia (to 32–34°C) controversial.
- If cerebral oedema uncontrolled, and donor liver identified, total hepatectomy may be considered.

Renal failure

- Occurs in 50% of cases, especially after paracetamol overdose.
- Important to involve renal team early.
- Management includes stopping all potentially nephrotoxic drugs, correcting hypovolaemia, and excluding/treating infection.
- Patient may require continuous haemofiltration. Standard indications include K^+ >6.0mmol/L, bicarbonate <15mmol/L and/or creatinine >400μmol/L, but may be considered earlier in patients with liver and renal failure.

Artificial liver support

- Range of ➲ liver support devices and techniques have been developed over last 30 years to act as 'bridge' to ➲ liver transplantation, or even allow time for native liver to recover spontaneously. None reliably effective to date, but the search goes on.
- Patients who are not suitable liver transplant candidates may benefit from plasma exchange. Further data awaited.

Prognosis and liver transplantation

- Spontaneous recovery more likely with hyperacute than subacute presentation. In patients with ALF and grade III–IV HE treated with medical therapy alone, survival 10–40%.
- In USA, 10% of paracetamol-induced ALFs require transplantation, compared with 30–50% of non-paracetamol causes. 5% of all liver transplants performed for ALF.
- With ➲ liver transplantation, survival from ALF now 60–80%, reinforcing need to consider and discuss case early.

Acute lower gastrointestinal bleeding

Definition

Blood originating from below ligament of Treitz (frequently quoted landmark: a fibromuscular band originating from right diaphragmatic crus and fixing duodenal–jejunal flexure).

Clinical presentation

- Haematochezia (fresh blood in the stool). Implies lower GI cause. Can occasionally result from very rapid bleeding from upper GI tract (will produce haemodynamic instability and usually ↑ blood urea).
- Blood in the bowel for over ~14h converts to black melaena. Up to 35% of patients with melaena have bleeding point distal to the duodenal–jejunal flexure, including right-sided colonic bleeding.
- Patient may be hypotensive and shocked without overt evidence of bleeding. Do not omit rectal examination.

Diagnosis

- History: Ask about prior episodes, and any history of haemorrhoids, inflammatory bowel disease, radiation, or iatrogenic causes (post-polypectomy bleeding can be delayed up to 10d).
- Establish whether any liver or renal disease, and drug usage (particularly antiplatelets, NSAIDs, anticoagulants).
- Ask whether blood mixed with or separate from stool. Bright red blood suggests anorectal cause. Change in bowel habit, pain, and weight loss suggest malignancy or inflammatory bowel disease.
- In West, common causes include bleeding from ➲ diverticula (40%), inflammatory conditions including infectious and ➲ ischaemic colitis, ➲ Crohn's disease and ➲ ulcerative colitis (20%), benign anorectal disease (10%), neoplasia and arteriovenous malformations including ➲ angiodysplasia.
- Rare causes include radiation, ➲ Meckel's diverticulum, and varices secondary to ➲ portal hypertension, particularly in rectum or at sites of surgical anastomoses.

Management

For most part, lower GI bleeds are less dramatic than upper GI bleeds: 90% stop spontaneously, 35% need transfusion and 5% urgent surgery. Mortality 2–4%. Resuscitation as for ▲ **acute upper GI bleeds** ▲.

Investigation

In patients who stop bleeding spontaneously, colonoscopy indicated either during admission or shortly thereafter. No clear evidence base for features that allow safe discharge from hospital, but might include:

- Haemodynamic stability, with no postural BP drop.
- No symptomatic anaemia, or untreated coagulopathy.
- Normal renal function, or stable chronic kidney disease.
- No melaena/mass on digital rectal examination.

In patients with continued bleeding, urgent diagnosis needed. If there is any doubt about lower GI source of blood, upper GI endoscopy vital (especially in patients with massive haematochezia and haemodynamic instability). Proctoscopy useful in diagnosing anorectal conditions, including haemorrhoids. Sigmoidoscopy may be useful if rectosigmoid source, but colonoscopy required for most lower GI bleeds.

Colonoscopy in acute lower GI haemorrhage

Intestinal lavage using nasogastric intubation followed by 4–6L of osmotic laxative such as Klean-Prep® allows adequate preparation. Traditional view that colonoscopy is impractical in severe bleeding is wrong, provided rapid cleansing used; identifies bleeding point in 45–90% of patients. Complication rate <2%. CT and direct selective angiography offer accurate diagnosis if bleeding brisk (>0.5ml/min). CT provides superior anatomical information if surgery planned; direct angiography may allow simultaneous therapy with embolization.

Treatment

- If haemodynamically compromised:
  - Establish good IV access (preferably 2× 14–16G cannulae in antecubital fossae).
  - Send bloods for FBC, clotting, U&Es, LFTs, and group & save. If significant bleed, cross-match 2–8U, according to severity, and always have 2U available for patients with ongoing bleeding.
  - Consider activating ▲ **major haemorrhage protocol** ▲.
  - Give 500ml of IV crystalloid (e.g. 0.9% saline) and review response. Repeat if necessary.
  - Insert urinary catheter if ongoing haemodynamic compromise, or renal impairment. Monitor hourly output.
  - Monitor vital signs every 15min-2h depending on stability.
  - Liaise with on-call surgical team.
- Blood transfusion strategy:
  - British Committee for Standards in Haematology recommend transfusion for 30–40% blood loss, to keep haematocrit >0.35.
  - Liberal transfusion (trigger Hb of 90–100g/L) associated with ↑ morbidity and mortality than more restrictive threshold of 70g/L, therefore latter recommended unless massive exsanguination.[3]

[3] Salpeter SR *et al.* (2014). *Am J Med* **127**: 124–31.

  - Still debate regarding optimum strategy for patients with cardiac disease. Some experts suggest better outcomes with Hb >100g/L, while other guidelines recommend restrictive approach.[4]
- Correct clotting abnormalities:
  - *Thrombocytopaenia* Give 1–2 pools platelets if count <50 × 10^9/L.
  - *Coumarins* (including **warfarin**) If INR >1.5 and ongoing bleeding, reverse with prothrombin complex concentrate + vitamin K 0.5–1mg IV. If bleeding stopped, consider vitamin K based on balance of thrombosis risk compared to further haemorrhage. If discontinuing warfarin indefinitely, give vitamin K 10mg IV.
  - *Direct oral anticoagulants* Some evidence prothrombin complex concentrate reverses **rivaroxaban** (but not **dabigatran** or **apixaban**). Monoclonal antibody (idarucizumab) that reverses dabigatran, and decoy receptor (andexanet alfa) that reverses rivaroxaban, apixaban, and edoxaban, developed. Limited availability and experience. Discuss with Haematology.
  - *Other causes of coagulopathy* If INR, APPT ratio or PT >1.5, give FFP 10–15ml/kg IV. Consider cryoprecipitate 10 units in patients with fibrinogen level <1.5g/L after FFP has been given.
- Achieving haemostasis:
  - Optimal therapy depends on identifying cause and site of bleed.
  - → **TERLIPRESSIN** may be effective in lower GI bleeds secondary to varices. Give 2mg stat IV (bolus over 3–5min), then 1–2mg every 4–6h for 72h. Can cause ischaemia, so contraindicated in patients with ischaemic ECG or history of vascular disease.
  - **Tranexamic acid** not routinely recommended (ineffective in HALT-IT trial[5] and ↑ risk of venous thromboembolism).
  - **Endoscopic therapy** If bleeding point identified, range of mechanical approaches available and effective, according to specific cause. Include haemostatic clips for bleeding vessels, loops for stalks of bleeding polyps, injection therapy (adrenaline 1:10,000), haemostatic powder sprays, and electrocoagulation therapy.
  - **Angiographic embolization** Coil embolization very effective in expert hands for arterial bleeds. Intra-arterial vasopressin can stop diverticular and angiodysplasia bleeding in up to 90%; rarely used as complications (particularly cardiovascular) in 5–15%.
  - **Surgery** Success depends on accurate preoperative localization.

Guidelines

BSG guidelines 2019 on lower gastrointestinal bleeding. 🖱 https://www.bsg.org.uk/wp-content/uploads/2019/02/gutjnl-2018-317807.pdf.

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[4] Qaseem A *et al*. (2013). *Ann Intern Med* **159**: 770–9.

[5] HALT-IT Trial Collaborators (2020). *Lancet* **395**: 1927-36.

Acute upper gastrointestinal bleeding

Definitions

Haematemesis refers to vomiting of blood and is indicative of haemorrhage occurring at any point from oesophagus to ligament of Treitz. Melaena is black, tarry stool, which smells sickly sweet. Occurs in 70–80% of upper GI bleeds, but may also present in right-sided colonic bleeds. Haematochezia is passage of red blood per rectum; although usually results from distal haemorrhage, important to remember that massive upper GI bleeds with swift transit can give this appearance.

Causes of upper GI bleeding

Incidence in UK ranges from 50 to 150/100,000/y. 30–50% of cases relate ➲ peptic ulceration, and 5–10% to varices. These conditions should be considered separately, because management differs. Other causes listed in Box 6.2, and in ~20% no cause identified.

Box 6.2 Causes of acute upper GI bleeding

- ➲ Peptic ulceration.
- Gastro-oesophageal varices (see also ➲ portal hypertension).
- ➲ Gastritis/gastric erosions.
- ➲ Oesophagitis.
- Duodenitis.
- ➲ Mallory–Weiss tear.
- ➲ Gastric antral vascular ectasia (GAVE) (‘watermelon stomach’).
- ➲ Dieulafoy lesions.
- ➲ Hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu syndrome).
- ➲ Gastrointestinal stromal tumour (GIST).
- ➲ Angiodysplasia.
- Portal hypertensive gastropathy.
- Upper GI tumours (e.g. ➲ oesophageal, ➲ gastric cancer).
- ➲ Aorto-enteric fistulae.
- Causes of ➲ haemobilia.

Initial assessment and management

Estimate extent of blood loss

- Ask about duration and volume of bleeding, colour, and frequency of haematemesis or melaena (e.g. 'two cupfuls, bright red vomit'). Was there associated lightheadedness, exertional dyspnoea or chest pain, or altered consciousness (suggesting large bleed)? 1L blood represents 20% blood volume.
- Has blood loss been witnessed? 'Coffee-ground vomit'—see it for yourself, as any dark vomitus tends to get this label and dipstick tests for blood are useless as they are almost always positive. Check what is meant by 'melaena' (examine bedpan, do rectal examination), as term often wrongly used to refer to any blood per rectum or dark stools due to iron supplementation). Haematochezia in presence of haematemesis suggests large bleed with rapid transit.
- Look for signs of hypovolaemia (pallor, cool peripheries, weak pulse, HR >100bpm, ↓ BP, ↓ JVP, confusion, ↑ respiratory rate). Measure postural drop in BP (>20mmHg systolic or >10mmHg diastolic fall after standing for 30s) and postural tachycardia (pulse rises by >30bpm), unless already hypotensive when supine.

Initial resuscitation (see Fig. 6.1)

- Establish good IV access (preferably 2× 14–16G cannulae in antecubital fossae—not single 20G line in dorsum of hand).
- Send bloods for FBC, clotting, U&Es, LFTs, glucose, group & save. Note Hb and haematocrit may not fall immediately, due to loss of whole blood, with fall only occurring after reactive plasma volume expansion and haemodilution. If significant bleed, cross-match 2–8U, according to severity, and always have 2U available if ongoing bleeding. Consider activating ▲ **major haemorrhage protocol** ▲.
- If hypovolaemic, give 500ml crystalloid (e.g. 0.9% saline) stat and review response. Repeat if necessary. Remember that fluid causes haemodilution (~10% ↓ in Hb for each litre of fluid). Nevertheless, only in very rare circumstances of massive exsanguination and delayed availability of cross-matched blood, does use of non-cross-matched blood (O negative) need to be considered.
- Do not attempt CVP line insertion prior to volume expansion, as wastes time and failure/complications (e.g. pneumothorax, carotid artery puncture) more likely. However, subsequent central line insertion should be considered for those with major haemorrhage if associated with cardiac failure or ischaemia, renal failure, failure to respond to resuscitation, or poor venous access.
- Insert urinary catheter in patients with large bleed, haemodynamic compromise, or renal impairment. Monitor hourly output.
- Monitor vital signs every 15min-2h depending on haemodynamic stability. Manage patient in appropriate medical setting (e.g. in massive haemorrhage, patients may need intubation to protect airway and level 2–3 care). Liaison with on-call surgical and anaesthetic team vital in major haemorrhage.
- Ensure nursing staff know patient must be kept NBM.

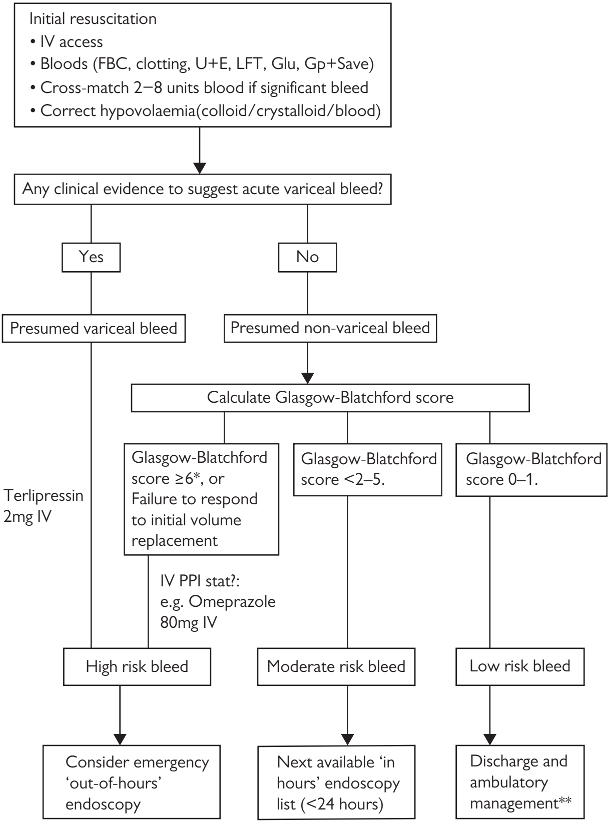
Initial resuscitation
• IV access
• Bloods (FBC, clotting, U+E, LFT, Glu, Gp+Save)
• Cross-match 2–8 units blood if significant bleed
• Correct hypovolaemia(colloid/crystalloid/blood)
Any clinical evidence to suggest acute variceal bleed?
Yes
No
Presumed variceal bleed
Presumed non-variceal bleed
Calculate Glasgow-Blatchford score
Glasgow-Blatchford score ≥6*, or Failure to respond to initial volume replacement
Glasgow-Blatchford score <2–5.
Glasgow-Blatchford score 0–1.
Terlipressin 2mg IV
IV PPI stat?: e.g. Omeprazole 80mg IV
High risk bleed
Moderate risk bleed
Low risk bleed
Consider emergency 'out-of-hours' endoscopy
Next available 'in hours' endoscopy list (<24 hours)
Discharge and ambulatory management**

Fig. 6.1 Initial management in acute upper GI bleeding. *See practice point, Box 6.3; **If other comorbidities and social factors allow.

Blood transfusion strategy

- The British Committee for Standards in Haematology recommend transfusion for 30–40% blood loss, to maintain haematocrit >0.35.
- Liberal transfusion (using trigger Hb of 90–100g/L) associated with ↑ morbidity and mortality than more restrictive threshold of 70g/L, therefore latter recommended unless massive exsanguination.[3]
- Still debate regarding optimum strategy for patients with cardiac disease. Some experts postulate better outcomes if keep Hb >100g/L, while other guidelines recommend restrictive approach.[4]
- In large volume haemorrhage, initiate ▲ **major haemorrhage protocol** ▲, to assist in arranging swift access to blood products.
- Correct clotting abnormalities:
  - *Thrombocytopaenia* Give 1–2 pools platelets if count <50 × 10^9/L.
  - *Coumarins* (including **warfarin**) If INR >1.5 and ongoing bleeding, reverse with prothrombin complex concentrate + vitamin K 0.5–1mg IV. If bleeding stopped, consider vitamin K based on balance of thrombosis risk to that of further haemorrhage. If decide to discontinue warfarin, give vitamin K 10mg IV.
  - *Direct oral anticoagulants* Some evidence prothrombin complex concentrate reverses **rivaroxaban** (but not **dabigatran** or **apixaban**). Monoclonal antibody (idarucizumab) that reverses dabigatran, and decoy receptor (andexanet alfa) that reverses rivaroxaban, apixaban, and edoxaban, developed. Limited availability and experience. Discuss with Haematology.
  - *Other causes of coagulopathy* If INR, APPT ratio or PT >1.5, give FFP 10–15ml/kg IV. Consider cryoprecipitate 10U in patients with fibrinogen level <1.5g/L after FFP has been given.

Decide on whether variceal or non-variceal cause most likely

- Identify patients with suspected variceal bleed:
  - Ask about history of liver disease and varices, and risk factors: alcohol excess, previous jaundice, IV drug misuse. Thrombophilia may suggest ➲ portal vein thrombosis.
  - Examine for signs of liver disease: jaundice, clubbing, palmar erythema, spider naevi, splenomegaly, ascites, encephalopathy.
  - Review bloods for deranged liver synthetic function. ↑ INR and ↓ plt suggestive but may coincide with large volume blood loss, so be wary of overinterpreting.
- Consider non-variceal causes:
  - Ask about previous episodes (➲ angiodysplasia?), preceding epigastric pain (➲ peptic ulceration?), reflux symptoms (➲ oesophagitis?), weight loss (malignancy?), medication (e.g. antiplatelets, NSAIDs, SSRIs, warfarin, heparin, direct oral anticoagulants), surgery (aortic graft, with risk of ➲ aorto-enteric fistula?), timing of bleeding (e.g. haematemesis after episodes of retching suggests ➲ Mallory–Weiss tear).
  - Examine for mucosal telangiectasia (➲ hereditary haemorrhagic telangiectasia), left supraclavicular lymph node (Virchow's node—suggests ➲ gastric/oesophageal cancer); scars of previous abdominal surgery.

Risk stratification

- Glasgow-Blatchford score (Table 6.3) used on presentation to help decide on need for inpatient admission and timing of endoscopy. Scores <1 can generally be investigated as outpatients, and <4 predicts low probability of requiring endoscopic therapy.[5]
- Rockall score (Table 6.4 and 6.5) post-endoscopy determines re-bleed risk. See ➲ Scoring systems for predicting outcomes in GI bleeds.

Suspected variceal bleed

Varices due to ➲ portal hypertension develop in 60% of patients with advanced cirrhosis (see ▶ Approach to cirrhosis and chronic liver disease). First bleed carries 25–50% mortality. Varices in distal oesophagus, gastro-oesophageal junction, or gastric fundus most usually bleed, but ectopic variceal bleeding (e.g. rectum, stomas, surgical anastomoses) may also occur.

- Risk factors for bleeding:
  - Large varices.
  - Endoscopic stigmata (e.g. 'red signs' on varices).
  - Bacterial infection.
  - Hepatic venous pressure gradient (HVPG) >16mmHg (see ➲ portal hypertension).
- Mortality related to severity of initial bleed, re-bleeding, infection, and comorbid cardiorespiratory or renal disease.

Ongoing management

- Summon gastroenterologist on-call immediately, as experienced staff essential. Involve anaesthetist, as risk of aspiration if patient encephalopathic, and may need intubation prior to endoscopy.
- Manage in HDU/ITU setting.
- If still hypovolaemic after initial fluid resuscitation, give blood if ready. Avoid overfilling, as may increase risk of re-bleeding (↑ portal venous pressure), but ensure adequate renal perfusion.
- Insert central line after initial fluid resuscitation, and preferably (but not essential) after clotting factors given. However, withhold insertion in: agitated patient (e.g. with ▲ **hepatic encephalopathy** ▲), if will delay essential emergency endoscopy, and in patient with large ongoing haematemesis who risks aspiration on lying supine.
- Give broad-spectrum IV cover (e.g. → CEFOTAXIME 1g bd + → METRONIDAZOLE 500mg tds IV for 5d). Bacterial sepsis common and associated with re-bleeding.
- Give → TERLIPRESSIN 2mg stat IV (bolus over 3–5min), then 1–2mg every 4–6h for 72h, or until bleeding stops. May cause ischaemia, so contraindicated in patients with ischaemic ECG or history of vascular disease. Helps control bleeding (79% of cases), and may ↓ mortality, but does not replace necessity of endoscopy. → OCTREOTIDE is an alternative if terlipressin not available/contraindicated.
- Give → PROTON PUMP INHIBITOR (e.g. pantoprazole 40mg IV), as ➲ peptic ulceration common in these patients and haemorrhage exacerbated by coagulopathy.

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[5] Stanley AJ *et al*. (2009). *Lancet* **373**: 42–7.

Endoscopy

Essential for definitive treatment and investigation. Perform within 6h, ideally after haemodynamically stable. Ensure anaesthetist present: **low** threshold for intubation prior to endoscopy. Protect yourself with facemask and double gloves if any risk of blood-borne virus transmission. At endoscopy, full examination of upper GI tract performed, as 26–56% of patients with ➲ portal hypertension and GI bleed have non-variceal cause (e.g. ➲ peptic ulceration).

Gastro-oesophageal varices

Variceal band ligation (VBL) should be performed. Involves placing rubber bands around varix base (see ➲ portal hypertension). Control of bleeding may occur through subsequent tamponade at gastro-oesophageal junction or development of variceal thrombosis. Sclerotherapy, involving needle puncture in or adjacent to varix, with injection of sclerosant (e.g. 5ml 5% ethanolamine oleate) may be used if VBL fails (or limited endoscopist experience of VBL); however, associated with 50% higher re-bleeding rate than with VBL.

Gastric varices

Account for ~10% of variceal bleeds, with ↑ rate of uncontrolled and re-bleeding and ↓ survival compared with gastro-oesophageal varices. VBL and sclerotherapy with standard sclerosants not effective. Variceal injection of cyanoacrylate ('super-glue') may be effective (90% initial haemostasis compared with 67% for ethanolamine), but has been associated with cerebral embolism due to glue migration. Thrombin may be effective and safer, but still high re-bleeding rates. In view of suboptimal haemostatic control with endoscopy or ➲ Sengstaken–Blakemore tube (SBT) inflation (especially if gastric varices not bleeding from high in gastric fundus), contact should be made early with specialist liver unit, for consideration of further management.

Uncontrolled bleeding/early re-bleeding

- 10–15% of patients have continuing variceal bleeding despite initial therapy. Early re-bleeding (recurrence within 5d of endoscopy) occurs in 30–50%, and is a strong predictor of death. Little benefit in performing >2 endoscopies in patients with ongoing bleeding.
- In patients with exsanguinating bleed that cannot be controlled endoscopically, ➲ Sengstaken–Blakemore tube (SBT) should be inserted. This controls acute bleeding from gastro-oesophageal varices in 90%, but recurrent bleeding occurs in 50% on deflation of balloon. Endotracheal intubation should be performed prior to tube insertion. Tube should be deflated and removed within 24h, and repeat endoscopy performed.
- If bleeding continues despite these measures, contact liver unit with a view to arranging ➲ TIPSS.
- Self-expanding metal stents, specific for management of variceal bleeding, show promise as an alternative to SBT or TIPSS.
- Recombinant factor VIIa 90μg/kg IV every 2h may have a role in stabilizing patients with massive variceal bleeding on a background of ➲ Child–Pugh B or C cirrhosis.

Further management

- Keep NBM for 4h following VBL.
- NG tube insertion should probably be avoided for 48h after VBL (but little evidence of absolute risk of dislodging bands).
- Retrosternal discomfort is common after endoscopic therapy, but usually responds to simple analgesia.
- Post-VBL/sclerotherapy ulceration may occur, and treated with → SUCRALFATE 1g qds and PPI (e.g. lansoprazole 30mg od). It is also a cause of re-bleeding, and then may be difficult to control.
- Prior to discharge, address the following:
    - Cause of varices, and severity and aetiology of any underlying liver disease. Re-bleeding less common and less severe in patients with non-cirrhotic portal hypertension (e.g. ➲ portal vein thrombosis), and recurrence in those with liver disease is strongly linked to ➲ Child–Pugh score.
    - Precipitant to bleed (e.g. infection, alcohol binge, NSAID use).
    - Treatment of underlying liver disease, and other manifestations of decompensation (e.g. ▲ **hepatic encephalopathy** ▲).
    - Need for secondary prophylaxis against further bleeds - do not forget this! See ➲ portal hypertension.

Suspected non-variceal bleed

Ongoing management

- 80% of non-variceal bleeds settle spontaneously.
- Glasgow-Blatchford score predicts need for endoscopic intervention (see Table 6.3). If <4, arrange endoscopy on next available 'in hours' list. If ≥4, patient has high-risk bleed and 'out-of-hours' emergency endoscopy should be considered.
- Inform on-call surgical team early about all high-risk bleeds (and encourage them to witness endoscopy—focuses minds if surgery needs to be considered).

Pharmacotherapy

- NICE guidelines 🔗 https://www.nice.org.uk/guidance/cg141 currently recommend withholding PPI therapy until after endoscopy, although this guidance is often debated (see Controversy box). Some adopt pragmatic approach of administering single dose of IV PPI (e.g. pantoprazole 40–80mg).
- PPI given post-endoscopy to high-risk patients (Forrest I–IIb, see Table 6.6) associated with improved clinical outcomes. High-dose IV PPI regimens reduce re-bleeding, but have minimal effect on mortality. In patients with high-risk bleeds, give omeprazole 80mg in 100ml 0.9% saline IV over 30min, then 8mg/h in same infusion (i.e. 10ml/h) for 72h. IV pantoprazole (same dose) is alternative.
- An oral regime (e.g. lansoprazole 30mg bd) may be similarly effective.[6] Expert opinion suggests IV regimens for Forrest I, IIa, and IIb bleeds, and oral regimens for IIc and III endoscopic findings.
- HALT-IT trial of >12,000 patients demonstrated no routine role for tranexamic acid, and an ↑ risk in venous thromboembolism.

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[6] Murthy S *et al.* (2007). *Dig Dis Sci* **52**: 1685–90.

Table 6.3 Glasgow-Blatchford score

Marker	Range	Score
Urea, mmol/L	<6.5	0
	6.5–8	2
	8–10	3
	10–25	4
	>25	6
Hb (♂), g/L	>130	0
	120–130	1
	100–120	3
	<100	6
Hb (♀), g/L	>120	0
	100–120	1
	<100	6
Systolic BP, mmHg	>109	0
	100–109	1
	90–99	2
	<90	3
Other parameters	HR >100/min	1
	Melaena	1
	Syncope	2
	Liver disease	2
	Heart failure	2

Table 6.4 Rockall score

Variable	Score			
	0	1	2	3
Age, y	<60	60–79	≥80	
Shock	Systolic BP >100mmHg, HR <100/min	Systolic BP >100mmHg, HR >100/min	Systolic BP <100mmHg	
Comorbidity	Nil major		Cardiac failure, IHD	Renal failure, disseminated malignancy
Post-endoscopy criteria				
Diagnosis	Mallory–Weiss tear, no lesion, no stigmata	All other diagnoses	Upper GI malignancy	
Major stigmata	None, or dark spots		Blood in upper GI tract, clot, visible vessel	

Table 6.5 Predicted mortality related to Rockall score

Score	Pre-endoscopy (%)	Post-endoscopy (%)
0	0.2	0.0
1	2.4	0.0
2	5.6	0.2
3	11.0	2.9
4	24.6	5.3
5	39.6	10.8
6	48.9	17.3
7	50.0	27.0
8+		41.1

Controversy. Timing of PPI administration

Although maintaining gastric pH >6 optimizes platelet aggregation and clot formation, no good evidence that giving PPIs to all suspected non-variceal bleeds prior to endoscopy ↓ mortality or re-bleeding (with caveat that studies may have had limited statistical power).[7] Nonetheless, same studies demonstrate that early PPI administration downgrades lesions by time of endoscopy, with consequently ↓ need for therapeutic intervention. As patients with high-risk lesions were then initiated on a 3d PPI infusion, early administration was also linked to reduced hospital stays.

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[7] Lau JY *et al*. (2007). *N Engl J Med* **356**: 1631–40.

Endoscopy

- Definitive procedure to make diagnosis and treat source of haemorrhage. Most accurately predicts prognosis, based on final Rockall score (Table 6.5) and Forrest classification (Table 6.6). Do not perform before attempts to resuscitate adequately.
- Consider emergency out-of-hours endoscopy in all high-risk bleeds (Glasgow-Blatchford score ≥4, with provisos—see Box 6.3). All other patients with significant bleed should be scoped within 24h.
- Endoscopic therapy indicated in patients with active bleeding or stigmata of recent haemorrhage (see Forrest classification, Table 6.6).
- Active bleeding and visible vessels should be treated; attempts to lift clot should be completed where possible; but clean ulcers and flat spots should be left.
- For treatment of non-variceal bleeding, use one of:
  - Mechanical method (e.g. clips) ± adrenaline.
  - Thermal coagulation + adrenaline.
  - Fibrin or thrombin + adrenaline.
- **Adrenaline** Works through combination of tamponade and vasoconstriction. Use 1ml aliquots of 1:10,000. Cardiovascular toxicity rare if <12ml used, although larger volumes (13–20ml) achieve less bleeding (15% vs. 30%) in high risk (Forrest I–IIa lesions).[8] Because of need for larger volumes in higher risk patients, some suggest using at concentration of 1:20,000. Adrenaline alone achieves only temporary haemostasis. Dual therapy reduces re-bleed rate and need for surgery, although does not change mortality, initial achievement of haemostasis, or transfusion requirements.
- **Clips** ideal for soft, small, easy to access lesions.
- Use **thermal coagulation** with caution as risk of perforation.
- Newer products (such as **haemostatic powder spray**) promising for active bleeding. Particularly useful in difficult to access areas (e.g. posterior duodenal bulb) or large areas of bleeding. Appears effective in isolated use, and in conjunction with traditional modalities, although more definitive data awaited.
- In patients with bleeding ➔ peptic ulcers, antral CLO test biopsy for ➔ *Helicobacter pylori* taken. Little evidence 'acute' eradication affects natural history of bleeding ulcer, but reduces recurrence. Note that pre-endoscopic → PROTON PUMP INHIBITOR therapy may cause false-negative result, so in these patients consider other modalities to diagnose or empirical treatment irrespective of result.

Box 6.3 Practice point: Scores and risk stratification

Don't be a slave to clinical grading systems. Prediction scores are useful, but never designed to replace clinical judgement. For example, an 80-year-old patient with pneumonia, who has an equivocal 'coffee-ground' vomit, may well have a raised Glasgow-Blatchford score. Out-of-hours endoscopy in this situation may not only be unnecessary, but dangerous. Emergency endoscopy indicated for those with large continuing bleeding: prediction scores should support, not replace, good clinical assessment.

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[8] Lin HJ (2002). *Gastrointest Endosc* **55**: 615–19.

Table 6.6 Forrest classification of re-bleeding risk

Class	Endoscopic finding	Re-bleeding rate (%)
Ia	Spurting artery	80–90
Ib	Oozing	55–80
IIa	Non-bleeding visible vessel	50–60
IIb	Adherent clot	25–35
IIc	Black spot in ulcer base	0–8
III	Clean ulcer base	0–12

Non-ulcer bleeding

- Endoscopic therapy may be effective in controlling bleeding due to ➔ Mallory–Weiss tear (although 50–80% stop spontaneously), and ➔ Dieulafoy lesions (96% controlled with primary haemostasis). ➔ Gastric antral vascular ectasia (GAVE) may be controlled with argon plasma coagulation (APC); trials ongoing with radiofrequency ablation and haemostatic powder.
- Patients with an aortic graft may present with sentinel bleed prior to catastrophic haemorrhage due to ➔ aorto-enteric fistula. Diagnosis made with CT ± emergency endoscopy with views round to duodenojejunal flexure. Emergency surgery carries high mortality (25–90%) and endovascular stenting may be necessary.

Post-endoscopy care

- Clear guidance on post-procedural management must be completed by the endoscopist. Include plan for management of re-bleeding (dependent on endoscopic findings and patient factors).
- Feeding of patients if haemodynamically stable and low risk for re-bleeding should be encouraged (allows pH to increase, promoting clot formation). Usually possible at 4–6h. Such patients should be given oral → PROTON PUMP INHIBITOR as soon as possible.
- In patients with Forrest I–IIb lesion, PPI infusion should be completed for 72h (e.g. omeprazole or pantoprazole 8mg/h IV).
- Check bloods daily until stable (FBC, U&Es).
- Re-bleeding indicated by new signs of hypovolaemia (compensatory tachycardia is an early sign), fall in Hb >20g/L over 24h, or development of fresh haematemesis or melaena (note: can persist for several days even after bleeding stopped, dependent on transit time).
- No clear role for repeating endoscopy in bleeders who have settled prior to discharge. However, all gastric ulcers need re-scoping and biopsy in 6wk to confirm resolution, as risk that ulcer is malignant.
- See ➔ peptic ulceration for treatment after recovery from bleed.

Endoscopy 'negative' upper GI bleeding

Further management depends on findings at first endoscopy:

- No blood and no lesion seen may be explained by:
  - Lesion already healed.
  - Bleeding distal to scope view (e.g. small bowel ➔ angiodysplasia, ➔ Meckel's diverticulum).
  - In patients with ongoing active blood loss >1ml/min consider CT angiography to identify source. Small bowel enteroscopy or capsule endoscopy alternatives, particularly if bleed rate slower.
- Blood seen but no lesion may be explained by:
  - Bleeding from unusual site (e.g. ➔ haemobilia; gastric fundal ➔ Dieulafoy lesion).
  - Blood obscuring adequate view on initial endoscopy.
  - In these cases, repeat procedure by senior endoscopist within 24h, along with pro-motility agents if significant obscuration (e.g. erythromycin 250mg IV, metoclopramide 10mg IV 20min prior to procedure). If possible haemobilia, have duodenoscope available for optimal views of papilla.

Failed endoscopy or re-bleed

- Consider repeat endoscopy in the first instance. Other modalities including interventional radiology and surgery should be explored if not controlled/further haemodynamic instability.
- Criteria for surgery not absolute, but crucial factors are **severity of bleed, endoscopic findings**, and **comorbidity**:
  - High-risk stigmata of re-bleeding on endoscopy, and failed endoscopic control (e.g. Forrest 1a lesion—spurting artery).
  - First re-bleed in patient >60y (elderly patients tolerate further episodes of hypotension and haemorrhage poorly, so require surgery earlier, not later, than younger patients). However, consider patient's 'biological age', remembering how many >60year-olds run the marathon!
  - Second re-bleed in patient <60y (rarely role for 3rd attempt at endoscopy, unless missed true lesion 1st time, treatment inadequate, or surgeon feels patient truly unfit for operation).
  - Ongoing bleeding after 6U blood in patient >60y, or 8U in <60y.
  - Surgery usually involves oversewing bleeding vessel in stomach or duodenum, vagotomy + pyloroplasty, or partial gastrectomy.
  - Alternative to surgery, particularly in patients with poor surgical prognosis, is angiography with embolization of feeding vessel.

Prognosis

Globally, mortality has changed little in past 20y (from 14% to 10%), although partially attributable to ↑ patient age and comorbidities. European mortality has had more significant improvement to 7%.[9]

Guideline

NICE guideline CG141 (2012) on management of acute upper gastrointestinal bleeding. 🖱 http://www.asge.org/uploadedFiles/Publications_and_Products/Practice_Guidelines/Management%20of%20ingested%20foreign%20bodies%20and%20food%20impactions.pdf.

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[9] Di Fiore F *et al*. (2005). *Eur J Gastroenterol Hepatol* **17**: 641–7.

Bowel obstruction

Mechanical or functional bowel obstruction prevents transit of luminal contents. Can be partial or complete. Causes subdivided into intraluminal, mural, or extramural structural lesions, or functional dysmotility of an otherwise patent bowel. Bowel proximal to level of obstruction dilates and accumulates secretions and swallowed air, resulting in significant fluid and electrolyte shifts. Progressive dilatation compromises blood flow, resulting in ischaemia and infarction.

Bowel strangulation is a surgical emergency, usually caused by oedematous bowel twisting around an adhesive band. Typically occurs with complete obstruction. When arising in patients with partial obstruction, generally only arises with Richter's hernia (where part of bowel circumference becomes trapped in hernia orifice). Left uncorrected, progresses to infarction and necrosis, intestinal perforation, peritonitis, and death. Mortality 100% untreated, 8% if operated within 36h (vs. 1% in patients undergoing surgery for simple mechanical obstruction), and 25% if surgery performed later.

Small bowel obstruction

Causes

- Adhesions (60%). Can occur from 4wk post-op; 3% of patients undergoing diagnostic laparotomy subsequently develop bowel obstruction. Rare following laparoscopy, although obstruction can occur through peritoneal defect caused by trochar placement.
- Incarcerated hernia.
- Neoplasia (particularly metastatic colonic and ovarian carcinoma).
- Stricturing ➔ Crohn's disease.
- ➔ Tuberculosis.
- ➔ Intussusception.
- ➔ Volvulus.
- Ischaemic or radiation strictures.
- ➔ Superior mesenteric artery syndrome.
- Foreign body, including bezoars.
- ➔ Gallstone ileus.

History

Abdominal distension, colicky central abdominal pain (constant focal pain is associated with strangulation), vomiting, constipation (after 12–24h). Ask about past medical history (including malignancy) and previous abdominal surgery.

Examination

Abdominal distension, tympanic percussion note, and high-pitched tinkling or absent bowel sounds (in mechanical and functional obstruction, respectively). Check hernial orifices. Clinical signs of volume depletion (↑ HR, ↓ BP, ↓ urine output). Pyrexia, tachycardia, and peritonism occur late, with strangulation and perforation.

Large bowel obstruction

Causes

- Neoplasia (60%). Left-sided lesions obstruct earlier.
- Adhesions.
- Hernias.
- ➲ Volvulus.
- Faecal impaction, severe constipation.
- ➲ Crohn's disease, ischaemic or radiation strictures.

History

Abdominal distension, colicky lower abdominal pain, absolute constipation (no passage of stool or flatus), vomiting (late feature). Abrupt onset of symptoms makes acute obstructive event (like volvulus) more likely. Chronic constipation, straining, and change in stool consistency are suggestive of carcinoma.

Examination

As for small bowel obstruction. Perform digital rectal examination to identify any low obstructing masses.

❗ Pitfall. Missed tumours

Be aware that the combination of femoral hernia + large bowel obstruction should prompt search for a colonic tumour. The hernia is frequently not the point of obstruction, but has manifested due to increased luminal pressure secondary to distal obstructing lesion.

Investigation

- Blood tests:
  - FBC, U&E, magnesium, clotting, G&S.
  - Venous blood gas if strangulation suspected. May reveal metabolic acidosis and raised lactate, although hypokalaemic alkalosis from vomiting can complicate interpretation.
- Imaging:
  - Plain AXR confirms obstruction in 75%. Signs include bowel distension (>3cm small bowel, >5cm large bowel) and air–fluid levels (only seen on erect/lateral decubitus films). Gas in rectum >24h after onset unusual in complete small bowel obstruction.
  - Erect CXR if perforation possible.

  - CT scan if mass lesion suspected or plain radiology equivocal, and to define transition point. Oral contrast not required as intraluminal fluid acts as natural contrast agent. Serrated appearance at point of obstruction suggests strangulation, as does bowel wall thickening, portal venous gas, and pneumatosis. Serial CT scans can be useful in patients managed conservatively.
  - Small bowel series or enema with water-soluble contrast (e.g. ➲ Gastrografin®, 100ml PO or PR) if CT non-diagnostic. Appearance of contrast within caecum at 24h following oral administration also predicts resolution, with sensitivity and specificity >95%. Plain AXRs required 6h, 12h, and 24h post-administration.
  - Consider requesting US or MRI small bowel in patients with known/suspected ➲ Crohn's disease and subacute obstruction.
- Endoscopy. Colonoscopy/ enteroscopy may be diagnostic and therapeutic if intraluminal obstruction or volvulus suspected, but should not delay surgery in peritonitic patient.
- Laparoscopy/laparotomy. If imaging studies do not identify source of obstruction.

Management

- Request surgical review.
- Make patient NBM. Insert wide-bore NG tube if ongoing vomiting.
- Replace fluids + electrolytes IV (particularly potassium and magnesium). Replace upper GI losses with 0.9% saline + 20–40mmol KCl.
- Prescribe analgesia and → ANTIEMETICS as required.
- Octreotide is a useful palliative agent if antiemetics insufficient.
- ➲ Gastrografin®. Adhesional bowel obstruction reported in some studies to respond to oral administration of gastrografin, as hypertonic and osmotically attracts water into bowel lumen, decreasing mural oedema and stimulating motility. Predicts need for operative management, and reduces need for surgery and hospital stay.[10]
- **Endoscopy**. Can be employed to remove foreign bodies, and decompress volvulus. Endoscopically-placed self-expandable mesh metal stents (SEMS) have particular role in acute obstruction secondary to malignant left-sided colonic tumours, especially in patients deemed palliative (i.e. not candidate for curative resection).
- **Surgery**. Laparotomy/laparoscopy ± resection indicated for:
  - Obstruction not resolving with 12–24h conservative management.
  - Incarcerated hernias.
  - Volvulus not responsive to endoscopic therapy.
  - Closed loop obstruction (obstruction at two sites producing isolated ischaemic segment, often with minimal signs).
  - Any evidence of ischaemic bowel or perforation.

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[10] Branco BC *et al*. (2010). *Br J Surg* **97**: 470–8.

Outcomes

Up to 80% of partial obstructions respond to conservative management, although 50% recur within 10y. 'Virgin abdomens' (i.e. in patients who have not previously had operation) usually progress to complete obstruction and surgery. Clinical improvement evidenced by return of normal bowel sounds, passage of flatus and ↓ in NG aspirate volume (to <150ml/4h). Mortality higher among patients managed surgically, largely associated with those with malignant obstruction (40% in-hospital mortality, thus manage conservatively if possible).

Acute colonic pseudo-obstruction

Refers to bowel amotility in the absence of mechanical obstruction.

Causes

- Postoperative (not limited to GI operations).
- Peritonitis (any cause).
- Intra-abdominal sepsis.
- Severe pneumonia, cardiac disease, or other systemic illness.
- Electrolyte disturbance (particularly hypokalaemia, hypocalcaemia, hypomagnesaemia).
- Trauma, especially spinal or retroperitoneal (affecting parasympathetic nerves).

Diagnosis

Based on history, examination (abdomen distended, tympanic and absent bowel sounds), and plain AXR (globally dilated large ± small bowel). Check FBC, U&E, calcium, magnesium, and CRP. Exclude underlying structural lesions (usually by CT) and toxic megacolon.

Management

- Conservative measures first: NBM, NG drainage if nausea/vomiting, and IV fluid and electrolyte correction. Regularly move patient to prone, elevated hip position. Correct underlying cause if possible. Avoid opiates, sedatives, and anticholinergics (impede bowel motility). Monitor progress with daily AXR.
- Neostigmine (2mg IV over 1–3min) helpful in 75% when symptoms persist >24–48h and caecal diameter >8–10cm. Patients should be cardiac monitored, with atropine available in case of bradycardia. Can be repeated daily, up to 3 times.
- Endoscopic deflation using suction, with flatus tube placed in transverse colon, if progressive colonic dilatation to >11cm. Bowel preparation should not be given and CO_2 used for insufflation.
- Surgery only required in 10% who have signs of peritonitis, or in whom conservative approaches fail.

Gastrointestinal foreign bodies

Data regarding management in this area are mainly based on retrospective case series and expert opinion. Before intervention, consider type of object ingested, organ involved, timing, and patient factors. Co-operation and sedation essential for safe removal. Likely to require anaesthetic support ± co-management with ENT team. General anaesthesia needed for children or uncooperative patients. Young, old, and cognitively impaired at greatest risk.

Swallowed foreign bodies

Ingestion of foreign bodies is most common in children, and in adults with psychiatric illness. Majority do not require any intervention and will naturally pass. Studies have shown that intervention is more likely to be needed if ingestion was intentional.

Clinical assessment

- Risk factors include history of previous intentional ingestion, congenital malformation, developmental delay, incarceration, and alcohol intoxication.
- Adults without cognitive impairment usually present explaining the course of the ingestion.
- Symptoms often occur a while after ingestion, and the location of discomfort correlates poorly with anatomical impaction. Do not forget that foreign bodies may impact in airway rather than oesophagus.
- If little history, look out for choking, refusal to eat, drooling (particularly with complete dysphagia), wheeze, and respiratory distress.
- Oropharyngeal and upper oesophageal impaction may present with neck swelling, crepitus, and tenderness.
- Sharp objects can perforate and are most likely to do so at the sites shown Fig. 6.2. Ileocaecal region is the most frequent site beyond the oesophagus. Examine for surgical emphysema, peritonism, or evidence of bowel obstruction.

Diagnosis

- Biplane radiographs (frontal and lateral) identify most foreign bodies, and provide information about site, number, and size. Some objects (aluminium, wood, fish bones) are radiolucent.
- Contrast studies generally not advised as high risk of aspiration, and coating foreign body can make endoscopic retrieval more difficult.
- If pain or swallowing difficulties persist, even with normal imaging, endoscopy should be considered.

Management

- Any indication of perforation or bowel obstruction should be managed surgically, and endoscopy should not be considered.
- Primary concern is airway support, as high risk of aspiration. Intubation should be considered prior to endoscopy, particularly in children, although conscious sedation suffices for most patients.
- Anyone unable to manage secretions should have emergency endoscopy. Otherwise, oesophageal foreign bodies or food impaction should be removed within 24h (as delay beyond this increases difficulty and likelihood of complications). If ingestion recent and object needs to be removed, lying patient in left lateral position reduces chance of passage through pylorus.
- Various devices can be used for retrieval of object. May be helpful to practice outside of patient, using object of similar size.
- Overtubes allow protection of airway, removal of multiple objects, and safe removal of sharp objects.
- Glucagon 1–2mg IV, or 0.02–0.03mg/kg in children, is suggested to relax lower oesophageal sphincter, but evidence limited.
- Once foreign body enters stomach, passes spontaneously in >90% within 4–6d. If remains >1wk should be considered for removal, endoscopically if in stomach or duodenum, or surgically if more distal.

Special considerations

- **Food bolus** Most common foreign body in Western world. Taking fizzy drink often advocated initially as aid to dislodging. Up to 33% of cases may be related to ➔ eosinophilic oesophagitis, so biopsies should always be taken from mid and lower oesophagus. Extraction may be en-bloc or piecemeal with use of snare or retrieval net.
- **Alkaline batteries** Liquefaction necrosis and perforation can occur rapidly when button battery is within oesophagus. Endoscopic removal should be completed as soon as possible. In stomach, aim for removal if plain X-ray shows separation of button components, or if button remains >24h. Once in small intestine, batteries tend to pass without complication within 72h.
- **Narcotic packets** Reported in both adult and paediatric cases. Packets may be seen on plain radiographs, but CT most sensitive if suspected. Sensitivity of urine toxicology ~35%. Leakage and rupture can often be fatal: endoscopic removal not advised and management of these cases is surgical, with medical support to manage toxidrome (Boxes 6.4 and 6.5).

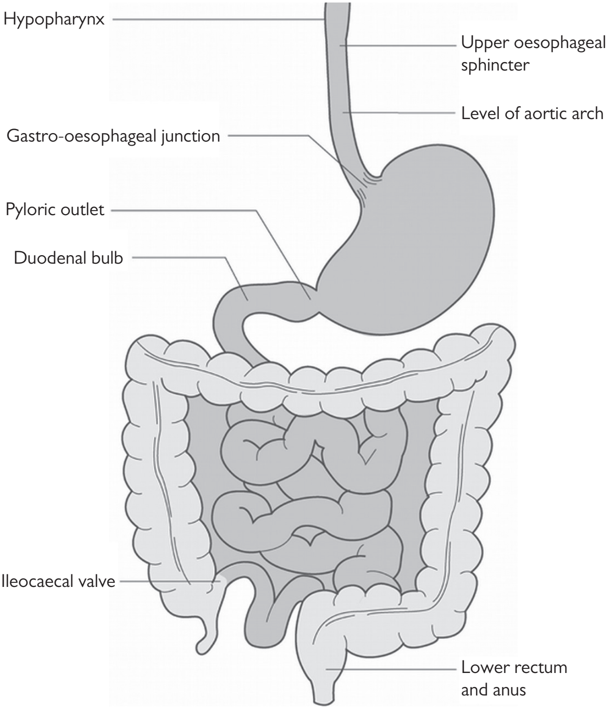

Hypopharynx
Upper oesophageal sphincter
Level of aortic arch
Gastro-oesophageal junction
Pyloric outlet
Duodenal bulb
Ileocaecal valve
Lower rectum and anus

Fig. 6.2 Common areas of luminal narrowing and angulation in GI tract leading to foreign body impaction.

Colonic and rectal foreign bodies

Range of objects retrieved is a tribute to the richness of human imagination. Retrieval usually possible. If beyond reach of sigmoidoscope and no evidence of perforation or obstruction, observe for 12–24h, and may descend to reachable level. Do not use enemas/cathartics. Sigmoidoscopy after removal necessary to exclude mucosal injury.

Box 6.4 Opiate overdose

Signs

Sedation, miosis, ↓ bowel sounds, and respiratory depression.

Management

Naloxone IV or IM. Give initial dose of 400µg. If no response after 1min, give a further 800µg. Repeat if still no response after another 60 seconds. Aim for full reversal of respiratory depression, then (as most opioids will have a longer half-life than naloxone) start an IV infusion with an hourly infusion rate equal to ~60% of the naloxone dose required to adequately reverse respiratory depression. Titrate to clinical effect. ❗ Infusions are not a substitute for frequent review.

Box 6.5 Cocaine overdose

Signs

Agitation, mydriasis, diaphoresis, tachycardia, and hypertension. Severe overdose can cause hyperthermia, seizures, and cardiovascular collapse with or without evidence of myocardial ischaemia.

Management

Immediate surgical removal indicated if packets leak, as no drug sufficiently antagonizes lethal effects of cocaine. Temporizing measures include benzodiazepines for agitation and seizures (diazepam 5–10mg PO or IV), sodium bicarbonate and lidocaine for ventricular dysrhythmias, and phentolamine or sodium nitroprusside for severe hypertension. β-blockers absolutely contraindicated.

Ethical considerations

Treat patient first. Informing police ± hospital administrator is a breach of confidentiality. Whether this would be justified in the public interest can be nuanced question, and best discussed with defence organization. Questioning patient must be sanctioned by a senior doctor. Patient must be made aware of their right to legal advice, through interpreter if necessary.

Guideline

American Society for Gastrointestinal Endoscopy (2011) guideline on management of ingested foreign bodies and food impactions.

Hepatic encephalopathy

Background

Hepatic encephalopathy (HE) is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting. Manifests with a wide spectrum of neuropsychiatric disturbances. Can be divided into overt (clinically evident) or minimal (requires neuropsychological testing). May develop in A (acute): acute/ hyperacute liver failure; B (bypass, following TIPS or portosystemic shunt surgery); or C (cirrhosis; see ► Approach to cirrhosis and chronic liver disease) patients. In patients with cirrhosis, HE can be episodic, persistent, or minimal.

Urea synthesis impaired in patients with liver disease. Therefore, brain (in particular astrocytes) and muscle act as alternative ammonia detoxification pathways. Astrocytes convert ammonia into glutamine. However, if brain receives high ammonia load then glutamine accumulates and astrocytes swell. Cerebral oedema follows with cytotoxic brain injury, manifesting as HE.

Clinical features

HE should be considered in any patient with liver disease and confusion or altered consciousness (see ► Approach to agitation and confusion in the GI patient). Subclinical HE may be difficult to diagnose, but has significant effect on lives of >30% of patients with cirrhosis. Diagnosis may require electroencephalography or psychometric testing. Clinical grading system applied to overt HE (Table 6.7), which in chronic liver disease carries poor prognosis (1y survival <50%).

Assessment

- Ask about ↑ sleepiness and reversal of normal sleep pattern. Has patient or friends/family noted change in personality or intellect?
- Examine for asterixis (coarse flapping tremor of hands extended at wrist—to elicit, ask patient to hold out arms in front of them and 'stop the traffic').

Investigations

- In patients with suspected HE, in whom diagnosis of liver disease not previously made, extent and cause of liver injury need to be established (see ► Approach to recent-onset jaundice and ► Approach to well patient with abnormal liver tests).
- Laboratory findings that suggest underlying liver disease include ↑ PT, ↑ Bn, and ↓ albumin (the three tests most indicative of poor liver function). ↓ platelets may suggest hypersplenism related to ➲ portal hypertension.

Table 6.7 Grading of hepatic encephalopathy

Grade		Features	Liver flap (asterixis)
Unimpaired		None	No
Minimal	Covert	Psychometric/neuropsychological alterations	No
I		Altered sleep rhythm Impairment of addition/subtraction Constructional dyspraxia (ask patient to copy 5-pointed star)	No
II	Overt	Lethargy/apathy Disorientation in time Personality changes	Yes
III		Somnolence to semi-stupor Confusion Bizarre behaviour	Yes
IV		Coma	Usually absent

- In patients with known cirrhosis, HE in association with worsening liver function requires search for additional liver insult (e.g. alcohol binge, acute viral hepatitis, constipation, new medication, ➔ portal vein thrombosis, ischaemia, ➔ hepatocellular carcinoma).
- Abdominal US or CT may show evidence of ➔ portal hypertension.
- Tests for HE *per se* relatively non-specific.
  - Blood (arterial or venous) ammonia levels ↑ in patients with ➔ portal hypertension, but correlation with HE is poor. Rarely contribute to making diagnosis, and can be normal in patients with encephalopathy or elevated in chronic liver disease patients who are otherwise well.
  - On EEG, normal waveform may be replaced by slower, higher-amplitude delta waves. Although similar changes seen in renal or respiratory failure, appearance may predate overt HE, and therefore has role.
  - Sensory evoked potentials remain a research tool.
- Brain imaging by CT or MRI does not help make diagnosis of HE but can exclude other causes of disturbed consciousness (e.g. intracerebral haemorrhage).
- ❗ Seek precipitant in all patients (see Box 6.6), including: septic screen (culture of blood, urine, sputum, ascites), exclusion of GI bleed (↓ Hb, melaena, serum urea disproportionately ↑ with respect to creatinine?), renal impairment, or constipation. In some patients, precipitating factor remains unidentified.

Box 6.6 Precipitants of HE and hepatic decompensation

- Progressive liver dysfunction.
- Additional liver insult (e.g. alcohol, ➲ hepatitis A/hepatitis E).
- ➲ Upper GI bleeding.
- ➲ Hepatocellular carcinoma.
- ➲ Spontaneous bacterial peritonitis.
- Intercurrent infection at other sites (e.g. pneumonia, urinary tract).
- Increased portosystemic shunt (e.g. new ➲ TIPSS formation).
- Electrolyte disorder (e.g. hyponatraemia).
- Dehydration (may be secondary to diuretics).
- Constipation.
- Renal failure.
- Drugs (e.g. opiates, diuretics).
- Non-concordance with treatment.

Management

- **Supportive care** for comatose patient essential. ITU assessment and admission necessary for grade III/IV HE, with consideration of endotracheal intubation if safe airway not maintained.
- **Treatment** of precipitants alone leads to resolution in >60%.
  - Give broad-spectrum antibiotics for overt sepsis (e.g. cefotaxime 1g IV tds, or piperacillin-tazobactam 4.5g IV tds), as well as for patients with variceal bleeding given association of sepsis with bleeding (see ▲ **acute upper GI bleeding** ▲) and potentially additive effects of sepsis and high gut protein load leading to HE.
  - Obsessive care of potential new sites of sepsis, such as IV cannulae and pressure areas, is vital.
  - Precipitant drugs should be stopped.
  - Acute kidney injury should be treated by controlling sepsis and ensuring adequate plasma expansion (see also ➲ hepatorenal syndrome).
- **Diet** Weak evidence for protein restriction in patients with HE. Patients often malnourished and may exacerbate problems. Protein intake should be maintained at 1–1.5g/kg/d, with transient reduction to 0.5g/kg/d only if overall treatment fails. Vegetable-based protein diets may be more effective than animal-based ones.
- **Bowel cleansing** helps reduce ammoniagenic substrates from gut. Give lactulose 30–50ml qds PO or via NG (no evidence that fine-bore NG tubes precipitate bleeding in patients with varices), aiming for passage of 2–4 soft stools/d. Improvement expected in 24–48h. Phosphate enemas should be used in patients with grade III/IV HE.
- Rifaximin 550mg PO bd (non-absorbable derivative of rifampicin) in conjunction with lactulose is as effective as lactulose and neomycin in HE, and may be better tolerated.
- Patients with portosystemic shunts and recurrent HE should be considered for embolization.
- Liver transplantation indicated for refractory HE.

Major haemorrhage protocol

Most hospitals now have established protocols in the event of a major haemorrhage, defined as blood loss >50% estimated blood volume (70ml/kg) in 3h, >100% in 24h or >150ml/min.

Basic resuscitation

If major haemorrhage suspected, initiate basic resuscitation:

- **Airway**. If at risk, fast bleep anaesthetist. Consider adjuncts (e.g. nasopharyngeal tube). Give high-flow oxygen via facemask with reservoir bag (unless contraindicated).
- **Breathing**. If ventilatory support required, put out crash call and initiate bag-valve-mask ventilation.
- **Circulation**. Establish IV access. Ideally 2 large-bore cannulae in antecubital fossae, but if challenging any access that can be achieved (including intraosseous) will do to initiate fluid resuscitation.

Who is contacted?

Call switchboard and ask to activate 'major haemorrhage protocol'. State patient location and which specialist teams also required (i.e. medical, surgical, obstetric). The following are then typically alerted:

- Haematology basic medical scientist, who should call back to ask how quickly blood required. Options are:
  - Immediate. ≈2U O-negative.
  - 10min from receipt of sample. Group-compatible.
  - 30min from receipt of sample. Fully cross-matched.
- ITU registrar.
- Haematology registrar. To authorize blood products and guide management of any coagulopathy.
- Porter.

What blood products will be available?

The following are typically automatically authorized:

- 6U packed red cells.
- 2 packs of FFP.
- 1 pool of platelets.

What tests need to be sent?

- FBC and cross-match minimum of 4U, although may need more depending on volume of blood loss (see Table 6.8).
- Coagulation screen.
- Fibrinogen. If low, indicates need for cryoprecipitate.

These may need to be rechecked until patient stable. Aim for platelets >50 × 10^9/L, INR<1.5 and fibrinogen >1g/L.

Estimating blood losses

Clinical features associated with increasing volumes of blood loss shown in Table 6.8. Class I and II patients should be volume resuscitated with crystalloid; class III/IV likely to need early blood products in addition.

Table 6.8 Estimating blood volume losses

	Class I	Class II	Class III	Class IV
Blood loss				
%	<15	15–30	30–40	>40
Volume, ml	<750	750–1,500	1,500–2000	>2,000
Vital signs				
HR, bpm	<100	100–120	120–140	>140
BP	Normal	Normal	🚱	↓
Pulse pressure	Normal/↑	↓	🚱	↓
RR, min^{-1}	14–20	20–30	30–40	>40
Urine output, ml/h	>30	20–30	5–20	<5
Mental status	Anxious	Anxious	Confused	Confused/ unconscious

*Adapted from ATLS guidelines.

Complications of blood transfusion

Assess for the following if transfuse ≥4U:

- Depletion of clotting factors and platelets. If ongoing bleeding:
  - If plt <50 × 10^9/L, give 1–2 pools platelet transfusion.
  - If INR >1.4, give 10–15ml/kg FFP + 10mg vitamin K IV.
  - If fibrinogen <1g/L, give 4–8U cryoprecipitate.
- Hypothermia. If core temperature <36°C, use blood warmers and warmed fluids.
- Acidosis. Ensure adequate correction of hypovolaemia.
- Hyperkalaemia:

  - Perform ECG to look for tall tented T waves, small P waves and QRS broadening. Give 10ml 10% calcium chloride if present.
  - Correct with 10U Actrapid insulin + 100ml 20% glucose IV over 30min.
- Hypocalcaemia. If develops, give 10ml of 10% calcium chloride.
- Disseminated intravascular coagulation (DIC). Evidenced by microangiopathic haemolytic anaemia (↓ Hb, ↑ Bn, ↓ haptoglobin, schistocytes on blood film), thrombocytopaenia, ↑ PT/APTT, ↓ fibrinogen, and ↑ D-dimer. Call haematologist for advice.

Oesophageal obstruction

Causes

- Foreign bodies (see ▲ **gastrointestinal foreign bodies** ▲).
- Tumour.
- Intramural oesophageal rupture (see ➲ intramural haematoma).
- Acute bolus obstruction. May occur in normal oesophagus after inadequate chewing, but more common in patients with pre-existing:
  - Oesophago-gastric cancer.
  - ➲ Oesophageal ring or ➲ oesophageal stricture.
  - Motility disorder.
  - Oesophageal stents or endoprostheses.
  - ➲ Eosinophilic oesophagitis.

Difficulty swallowing (dysphagia) is discussed in ► Approach to the mouth and swallowing.

Clinical features

Ask about, and look for:

- **Pain** Oesophageal pain can mimic that of acute myocardial infarction but close temporal relation with eating, combined with dysphagia, usually helps distinguish the two.
- Patient's ability to **swallow own saliva**.
- **Duration of symptoms**.
- **Predisposing disease** Stricture, carcinoma, ➲ oesophageal ring.
- **Triggering factors** Classically steak and bread, but also tablets.
- **Dehydration**.
- **Weight loss** Suggests malignancy.
- **Supraclavicular nodes** e.g. ➲ gastric cancer.
- **Complications** Aspiration, perforation.

Investigation

- Bloods:
  - FBC. Anaemia may suggest chronic bleeding lesion.
  - U&E for dehydration, electrolyte disturbance.
- Imaging:
  - CXR to look for mediastinal fluid level or aspiration pneumonia.
  - CT chest if extrinsic compression possible.
- Endoscopy. Preferred to contrast swallow, which risks aspiration, but must be done by experienced endoscopist.

Management

- Contact on-call endoscopist.
- Carbonated drinks can occasionally dislodge food bolus.
- Glucagon 1–2mg IV, repeated after 5 and 10min if necessary, sometimes trialled (relaxes lower oesophageal sphincter), but often not effective.
- IV fluids.
- Endoscopic removal of bolus can be followed immediately by dilatation of any strictures, or biopsy of any suspicious mucosal lesion.
- If oesophageal stent or prosthesis in place, assessment of tumour ingrowth, overgrowth, or stent migration essential.
- Endoscopic placement of fine-bore feeding tube may be necessary after disimpaction if dilatation delayed.
- IV antibiotics for aspiration (e.g. → CEFUROXIME 750mg tds, → METRONIDAZOLE 500mg tds, or co-amoxiclav 1.2g tds).

Oesophageal rupture

Causes

- **Spontaneous** Usually caused by vomiting. First described by Herman Boerhaave in 1724 (see ➔ Boerhaave's syndrome): following a large meal Grand Admiral of Holland Baron Jan von Wassenaer started vomiting, developed severe abdominal pain, and later died; autopsy revealed a large tear in the oesophagus.
- Also reported with foreign bodies (such as bones and batteries), caustic ingestion, and trauma.
- **Iatrogenic** Up to 50% of cases caused by medical procedures (see also p. 204). Oesophagus said to be at ↑ risk because lacks a serosal layer (Table 6.9).
- ➔ Intramural haematoma can result from sudden increases in intraoesophageal pressure.

Table 6.9 Risk of oesophageal perforation due to medical procedures

Procedure	Risk of perforation	Site and comments
Rigid oesophagoscopy	1 in 10	Proximal oesophagus (associated with arthritic cervical spine or pharyngeal pouch)
Flexible endoscopy	<1 in 1,000	Usually at intubation or in attempted passage through oesophageal stricture, or in presence of oesophageal pouch
Balloon dilatation of achalasia	<2% with balloons <35mm Up to 5% with 40mm balloon	
Dilatation of malignant stricture	Up to 10% in old series using rigid prostheses; much less with self-expandable metal stents (SEMS)	

Diagnosis

Early diagnosis crucial. Clinical signs may be minimal as perforation usually small, patient often fasted (and sedated), and instruments should be clean if not sterile. Perforation may be apparent at time of procedure, but surgical emphysema, tachycardia, cyanosis, and pain (especially odynophagia) should arouse suspicion.

Radiology

Plain films may show pneumomediastinum ± pneumothorax ('V-sign of Naclerio', outlining diaphragm on CXR), pneumoperitoneum, or left pleural effusion; but can be normal. Late changes of air–fluid collections better assessed by CT. Contrast studies using water-soluble media conventionally used to define site and length of perforation.

Management

- **Get a surgical opinion** Mortality high (>90% in spontaneous rupture), and non-operative approaches apply only to specific situations and require experience. If perforation small (<1cm), recognized early, and not associated with gross contamination, conservative management can be successful and includes NBM, IV broad-spectrum antibiotics (e.g. → CEFUROXIME 750mg tds + → METRONIDAZOLE 500mg tds), and parenteral feeding. Exceptions are perforations into abdominal or pleural cavities, which mandate surgical repair.
- Spontaneous ruptures usually associated with gross contamination, and surgery generally advised.
- Perforations associated with balloon dilatation often contained within oesophageal wall and may be managed without surgery.
- If perforation caused at endoscopy, closure of perforation may be feasible with immediate endoscopic expertise. Depending on site and extent, options include endoscopic clipping, or insertion of a fully covered SEMS.
- **Perforation of oesophageal cancer** at endoscopy is a difficult problem, with higher mortality (up to 50%). Perforation site can sometimes be protected by fully covered SEMS. Give antibiotics and start nutritional support.

Clinical factors determining outcome

- Delay in diagnosis.
- Size of hole.
- Degree of soiling of mediastinum or pleural cavity with stomach contents.

Appendices

Appendix 1: CT images of the abdomen *708*
Appendix 2: Useful contact numbers and links *712*
Appendix 3: Normal laboratory ranges *714*

Appendix 1: CT images of the abdomen

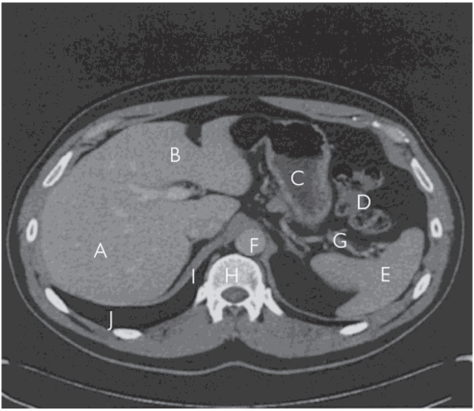
Normal abdominal CT

There is never a substitute for sitting down and reviewing imaging with your friendly radiology colleagues, but it is often worth knowing where normal anatomy resides on an abdominal CT scan.

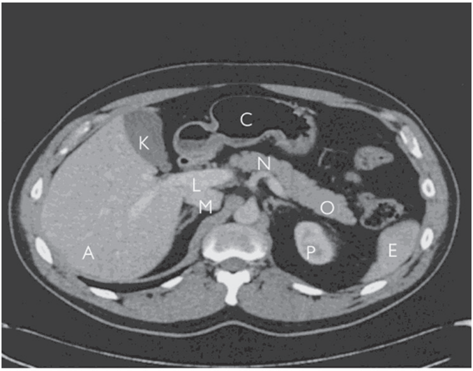
A few tips

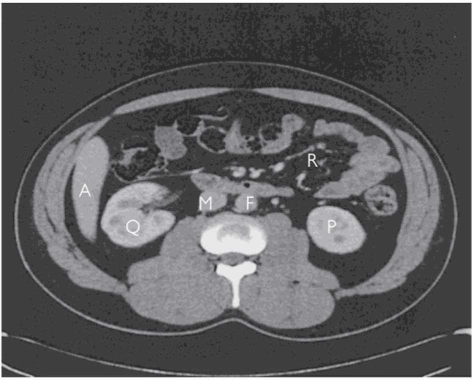
- Film usually taken with patient supine and viewed from caudal position (i.e. from below, with right side of abdomen appearing on the left).
- Air, water, and fat appear dark/black on CT.
- Oral contrast (positive: e.g. dilute barium; negative: e.g. water) may be given to delineate stomach and upper GI tract from surrounding structures.
- Structures with high density (e.g. bones, calcified vessels) appear white.
- After IV contrast, images can be taken during arterial phase (bright aorta and branches) and venous phase (bright hepatic and portal veins).

The following sequence of CT scans shows sequential cuts through the abdomen from diaphragm to pelvis.

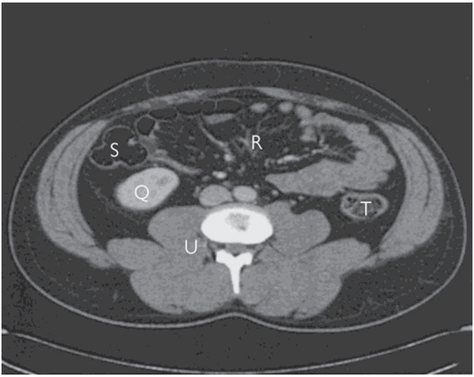


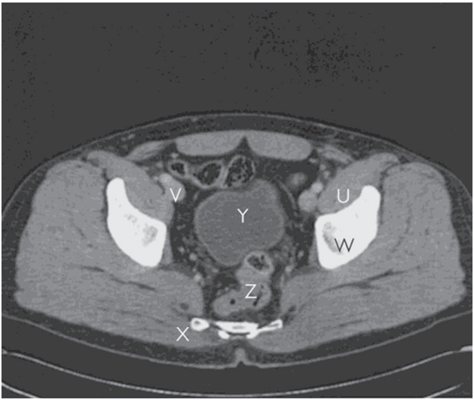
A: Right lobe of liver	F: Aorta
B: Left lobe of liver	G: Splenic artery
C: Stomach	H: Vertebra
D: Colon (splenic flexure)	I: Diaphragmatic crura
E: Spleen	J: Right lung base





K: Gallbladder	O: Tail of pancreas
L: Portal vein	P: Left kidney
M: Inferior vena cava	Q: Right kidney
N: Body of pancreas	R: Small bowel mesentery





S: Ascending colon

T: Descending colon

U: Psoas muscle

V: External iliac vessels

W: Acetabulum

X: Sacrum

Y: Bladder

Z: Rectum

Appendix 2: Useful contact numbers and links

UK liver transplant units

King's College Hospital, London	0203 299 5812
Royal Free Hospital, London	0207 794 0500
Addenbrooke's Hospital, Cambridge	01223 245 151
Freeman Hospital, Newcastle upon Tyne	0191 233 6161
Queen Elizabeth Hospital, Birmingham	0121 472 1311
St James's University Hospital, Leeds	0113 243 3144
Royal Infirmary of Edinburgh	0131 536 1000

Poisons unit

National Helpline	0844 892 0111

Tropical and infectious diseases

London	0207 388 9600
Liverpool	0151 708 9393
Glasgow	0141 211 1000

Virus Reference Laboratory

Central Public Health Laboratory, London	0208 200 4400

GI and hepatology societies

- American Association for the Study of Liver Disease (AASLD): 🖱 *www.aasld.org*
- American Gastroenterology Association (AGA): 🖱 *www.gastro.org*
- Association of Coloproctology of Great Britain and Ireland (ACPGBI): 🖱 *www.acpgbi.org.uk*
- British Association for the Study of the Liver (BASL): 🖱 *www.basl.org.uk*
- British Society of Gastroenterology (BSG): 🖱 *www.bsg.org.uk*
- European Association for the Study of the Liver (EASL): 🖱 *www.easl.eu*
- European Crohn's and Colitis Organization (ECCO): 🖱 *www.ecco-ibd.eu*
- European Society of Coloproctology (ESCP): 🖱 *www.escp.eu.com*
- European Society of Gastrointestinal Endoscopy (ESGE): 🖱 *www.esge.com*
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): 🖱 *www.niddk.nih.gov*
- Pancreatic Society of Great Britain and Ireland (PSGBI): 🖱 *www.psgbi.org*
- United European Gastroenterology (UEG): 🖱 *www.ueg.eu*

Patient support and charitable organizations

- Barrett's Oesophagus UK: 🖱 *www.barrettsfoundation.org.uk*
- British Liver Trust (BLT): 🖱 *www.britishlivertrust.org.uk*
- Cancer Research UK (CRUK): 🖱 *www.cancerresearchuk.org*
- Coeliac UK: 🖱 *www.coeliac.org.uk*
- Crohn's and Colitis UK: 🖱 *www.crohnsandcolitis.org.uk*
- Guts UK: 🖱 *https://gutscharity.org.uk/*
- PBC Foundation: 🖱 *www.pbcfoundation.org.uk*
- PSC Support: 🖱 *http://www.pscsupport.org.uk/*
- UK Transplant: 🖱 *www.uktransplant.org.uk*

General clinical information

Cochrane Library: 🖱 *www.cochranelibrary.com*
National Institute for Health and Care Excellence (NICE): 🖱 *www.nice.org.uk*
Medical eponyms: 🖱 *www.whonamedit.com*

Appendix 3: Normal laboratory ranges

Haematology	
Haemoglobin	Male: 130–180g/L Female: 115–160g/dL
Mean cell volume (MCV)	80–99fL
Haematocrit	Male: 0.37–0.50 Female: 0.33–0.45
White blood cells	3–10 × 10^9/L
Neutrophils	2–7.5 × 10^9/L
Lymphocytes	1.2–3.65 ×10^9/LC
Eosinophils	0–0.4 × 10^9/L
Platelets	150–400 × 10^9/L
Erythrocyte sedimentation rate (ESR)	<20mm/hr

Biochemistry	
Sodium	135–145mmol/L
Potassium	3.5–5.1mmol/L
Urea	1.7–8.3mmol/L
Creatinine	Male: 66–112μmol/L Female: 49–92μmol/L
Calcium	2.2–2.6mmol/L
Phosphate	0.87–1.45mmol/L
Glucose	3.6–5.8mmol/L
Bicarbonate	22–29mmol/L
C-reactive protein (CRP)	<5mg/L
Amylase	28–100U/L
Total immunoglobulin (Ig)	15–35g/L (IgG: 7–16g/L; IgA: 0.7–4g/L; IgM: 0.4–2.3g/L)
Cholesterol	<5mmol/L
Triglycerides	0<2.3mmol/L

Liver function tests	
Bilirubin	0–20μmol/L
Alanine aminotransferase (ALT)	10–50IU/L
Aspartate aminotransferase (AST)	0–37IU/L
Alkaline phosphatase (ALP)	40–129IU/L
γ-glutamyl transferase (γGT)	10–71IU/L

Liver function tests	
Total protein	63–83g/L
Albumin	34–50g/L
Ammonia	11–32μmol/L
Haematinics	
Serum iron	10.6–28.3μmol/L
Ferritin	Male: 30–400μg/L Female: 13–150μg/L
Total iron binding capacity (TIBC)	41–77μmol/L
Red cell folate	100–600μg/L
Serum folate	≥ 3ng/mL
Vitamin B_{12}	191–663pg/mL
Stool tests	
Faecal calprotectin	<50μg/g
Faecal elastase	>200μg/g

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